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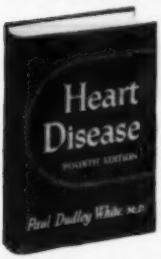

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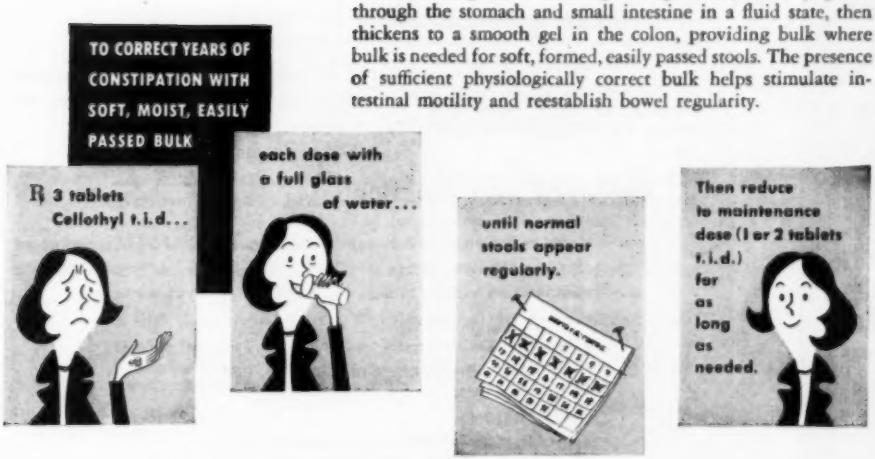
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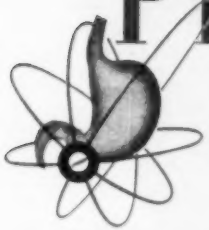

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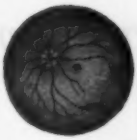

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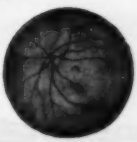

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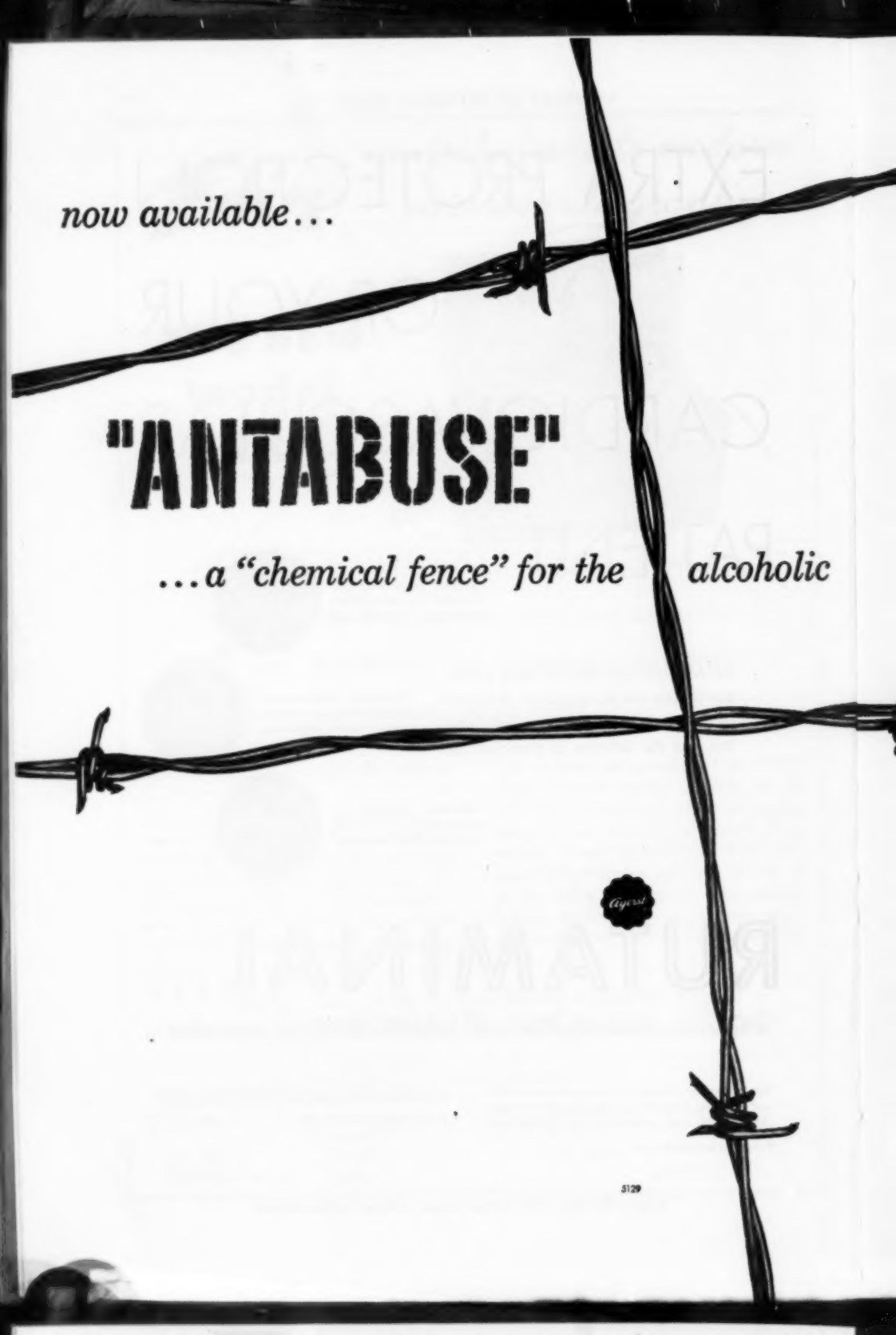
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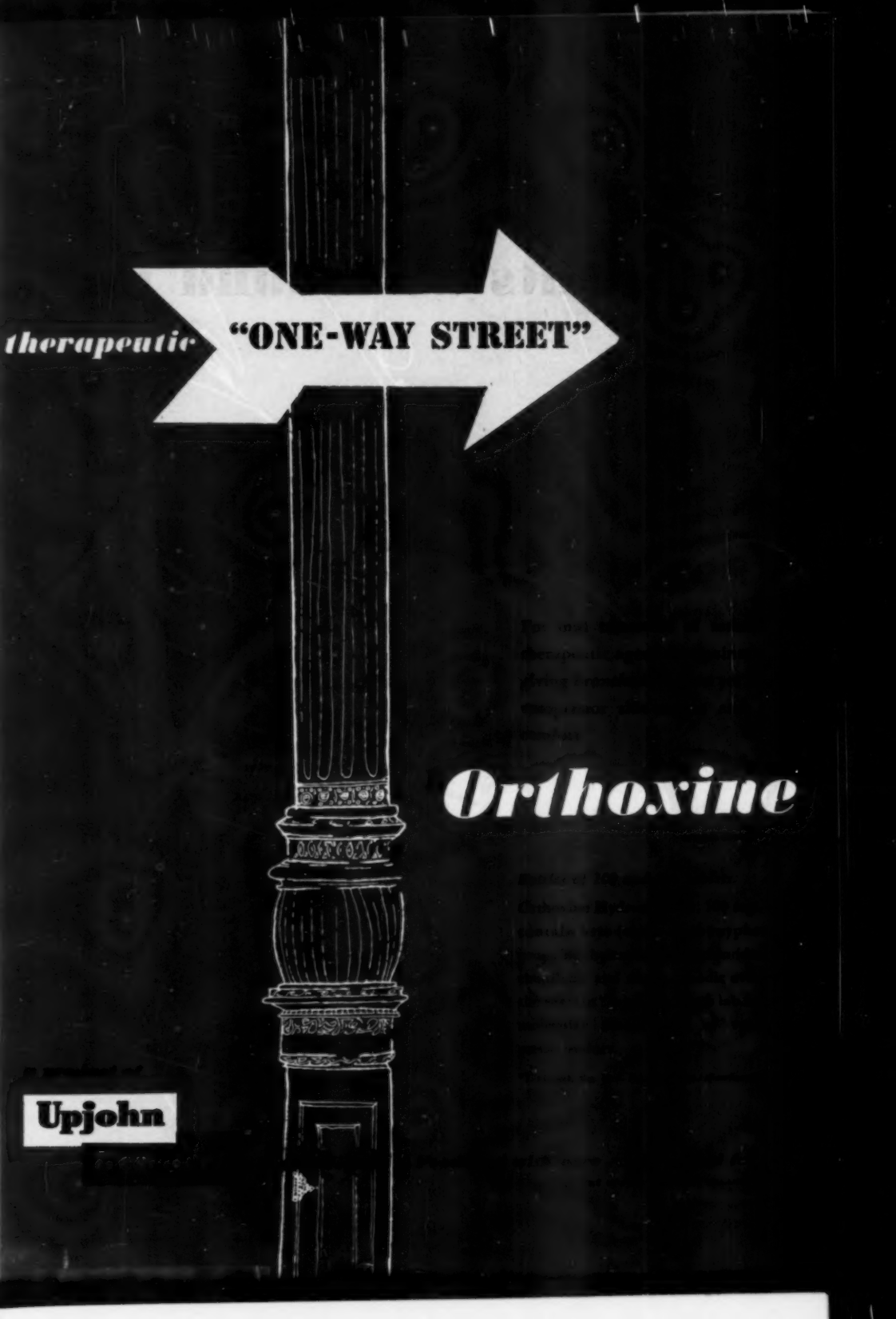
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relief from pain, cramps, general discomfort due to functional gastrointestinal spasm. In clinical studies,[1, 2, 3] BENTYL gave gratifying to complete relief in 308 of 338 cases, yet was "... virtually free from undesirable side effects."[3]

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Each capsule or teaspoonful syrup contains:

BENTYL . . . . . **10 mg.**
For comfortable relief of nervous indigestion

BENTYL . . . . . **10 mg.**
with **PHENOBARBITAL** . . . . . **15 mg.**
When synergistic sedation is desired

DOSAGE

ADULTS: 2 capsules or 2 teaspoonfuls syrup 3 times daily, before or after meals. If necessary, repeat dose at bedtime.

IN INFANT COLIC: ½ to 1 teaspoonful syrup 3 times daily before feeding.[4]

Merrell
1828

New York • CINCINNATI • Toronto

1. Hock, C. W.: J. Med. Assn. Ga. 40:22, 1951. 2. Hufford, A. R.: J. Mich. St. Med. Soc. 49:1368, 1950. 3. Chamberlin, D. T.: Gastroenterology 17:224, 1951. 4. Pakula, S. F.: To be published.

Trade-mark "Bentyl" Hydrochloride

Accepted for Advertising
in The Journal of
The American Medical
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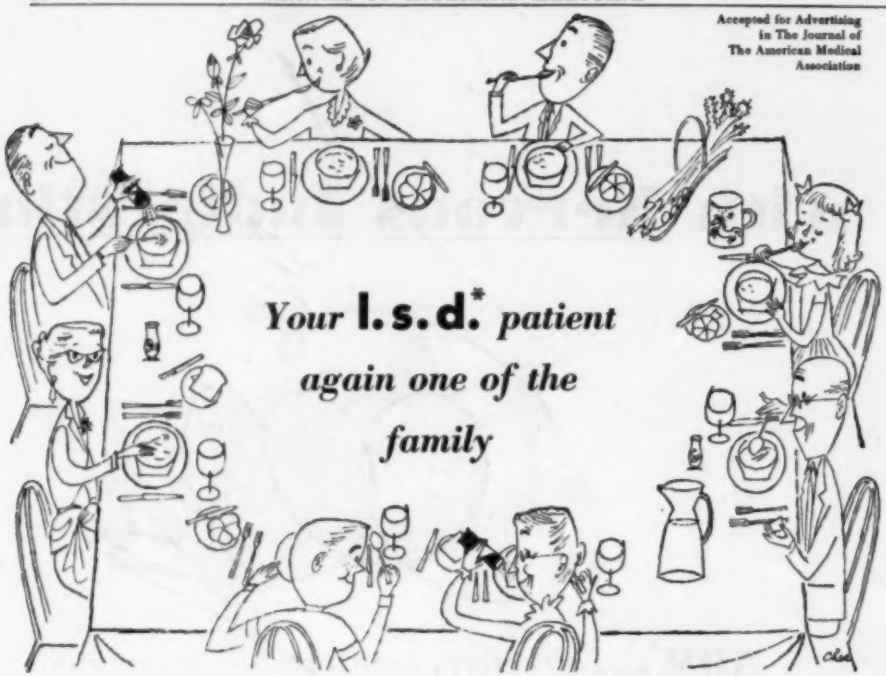

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1. Rimmerman, A.B., and Halpern, A.: A comparative study of sodium-free salt substitutes. Am. Pract. & Dig. Treatment 2:168 (February) 1951.
2. Fremont, R.E.; Rimmerman, A.B., and Shaftel, H.E.: The occurrence and management of the low potassium state with patients on the low sodium diet. Postgraduate Med. 9:—(September) 1951.

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1. Thorn, G. W., and Tyler, F. H.: *Med. Clin. North America*, 31:1081, Sept. 1947.

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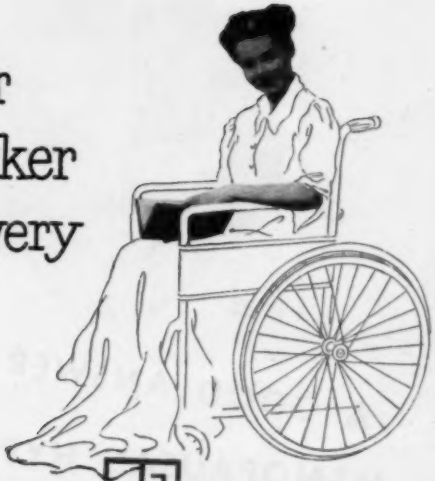

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When nutritional intake is impaired, restoration of health and return to work may be retarded for months unless the indispensable water-soluble vitamins are rapidly replaced. Correction by diet alone is "a slow, tedious and costly process."*

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	Nicotinamide	100 mg.		
	Folic Acid	2.5 mg.	Vitamin C	150 mg.

Dosage: 1 or 2 Kapseals daily. ***Packaging:*** Bottles of 100 and 1000.

*Spies, T. D.: Rehabilitation Through Better Nutrition, Philadelphia, W. B. Saunders Co., 1947, p. 62.

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KHELLOYD ..... 50 mg.
Phenobarbital ..... ¼ gr.

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*Scott, R. C., and Seiwert, V. J., to be published.

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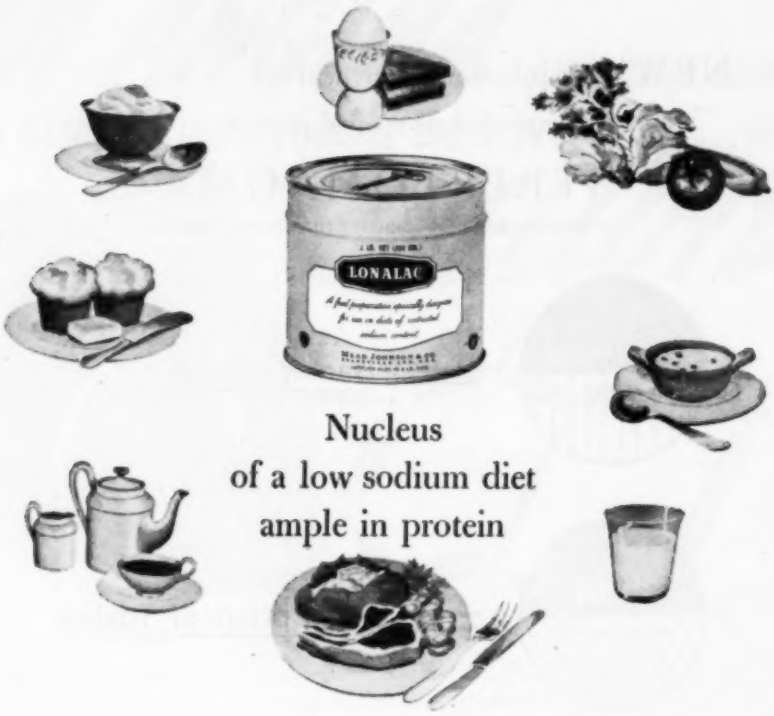

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relieves stiffness and discomfort
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Oral dosage in rheumatic disorders and allied conditions:

Initial dose is 1.5 to 2.0 Gm. or more, depending on the weight of the patient. To be followed by 0.5 to 0.75 Gm. every three hours as long as discomfort continues.

Tolserol should be given after meals. If given between meals, the patient should drink ⅓ glass of milk or fruit juice before taking Tolserol. This is desirable because the administration of large doses when the stomach is empty has caused some weakness, giddiness, syncope, or gastric distress in a few patients. Some clinicians, however, prefer to give Tolserol when the stomach is empty in order to obtain a rapid effect; in such cases, the patient should be under observation.

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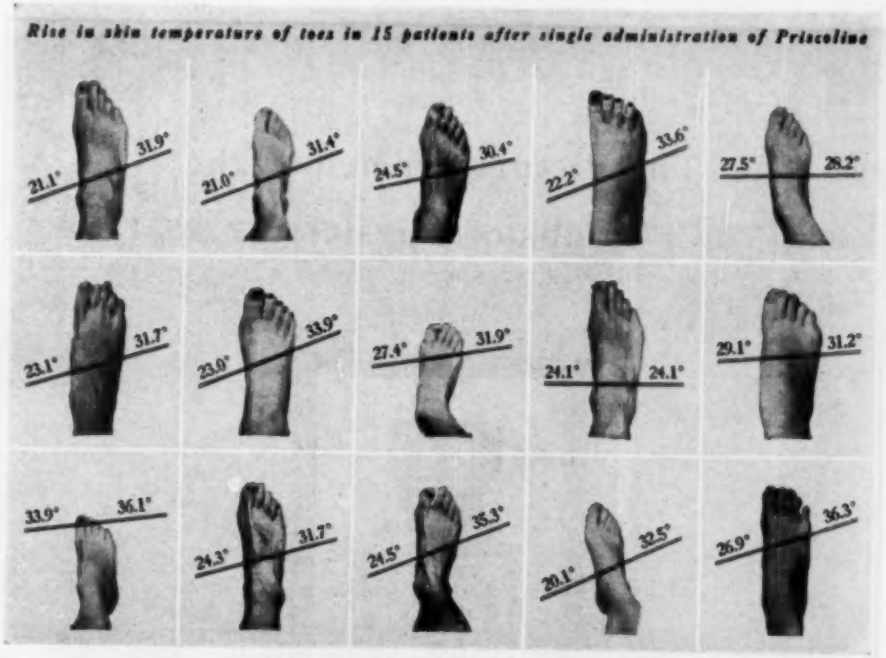

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1. Ready, W. J.: J. of Lab. & Clin. Med. 37:385 (March) 1951.

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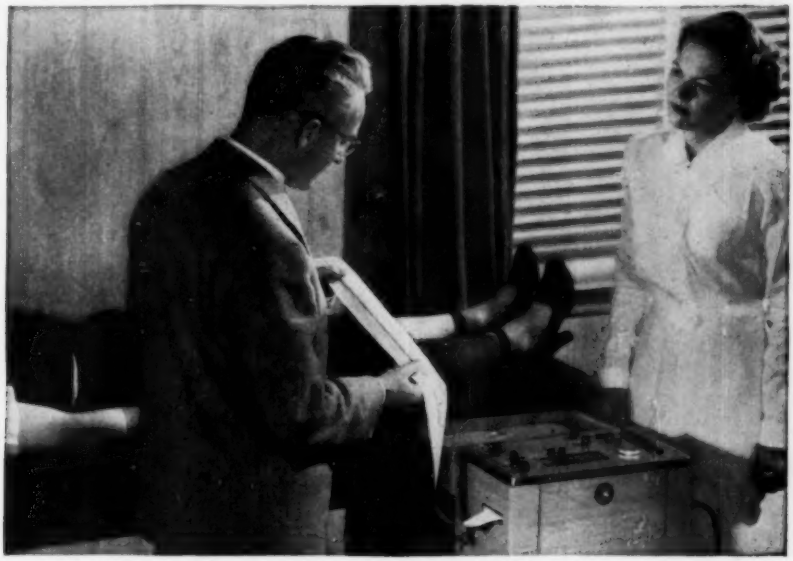

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*Burke, G. E., and Wright, Irving S.: Circulation 3:164, 1951.

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*Kramer, P. and Ingelfinger, F. J.: Med. Clin. North Amer. 32:1227, 1948.

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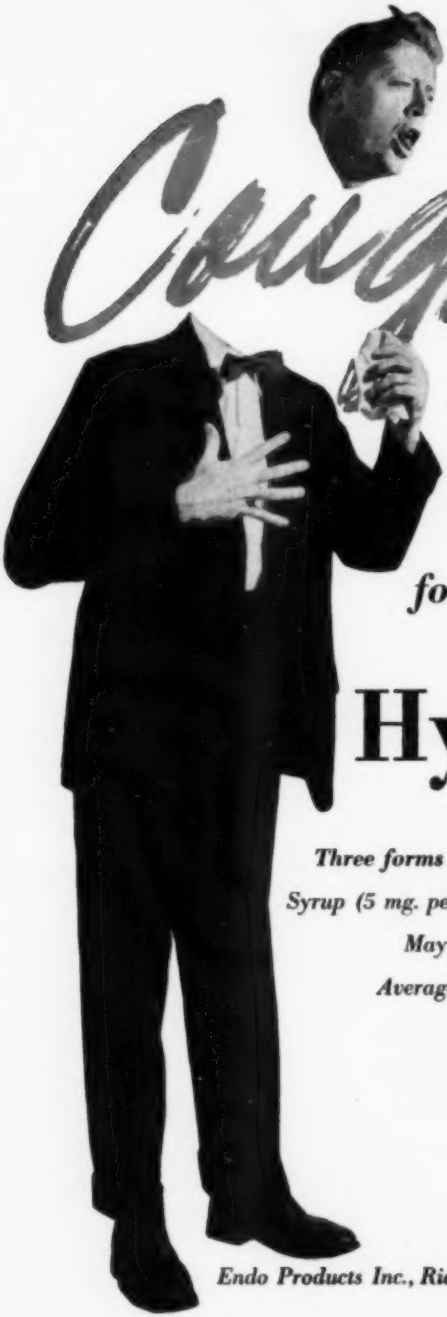

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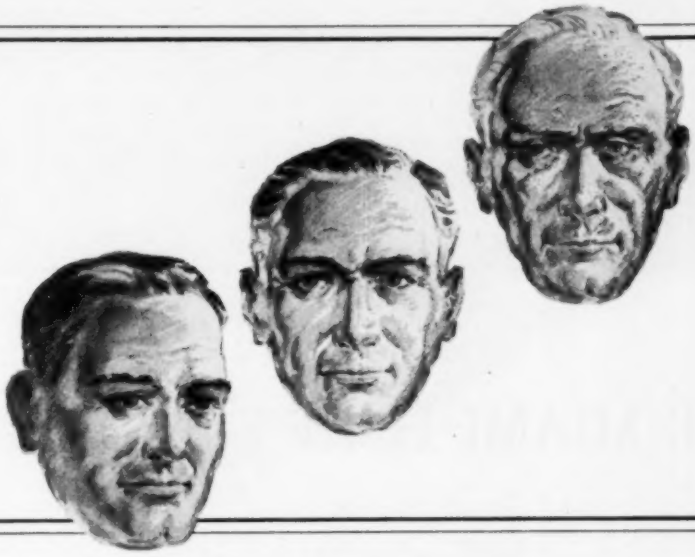

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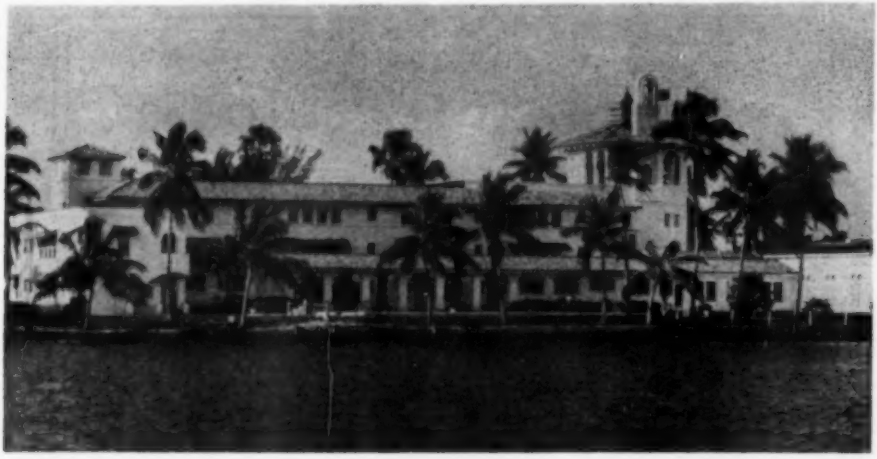

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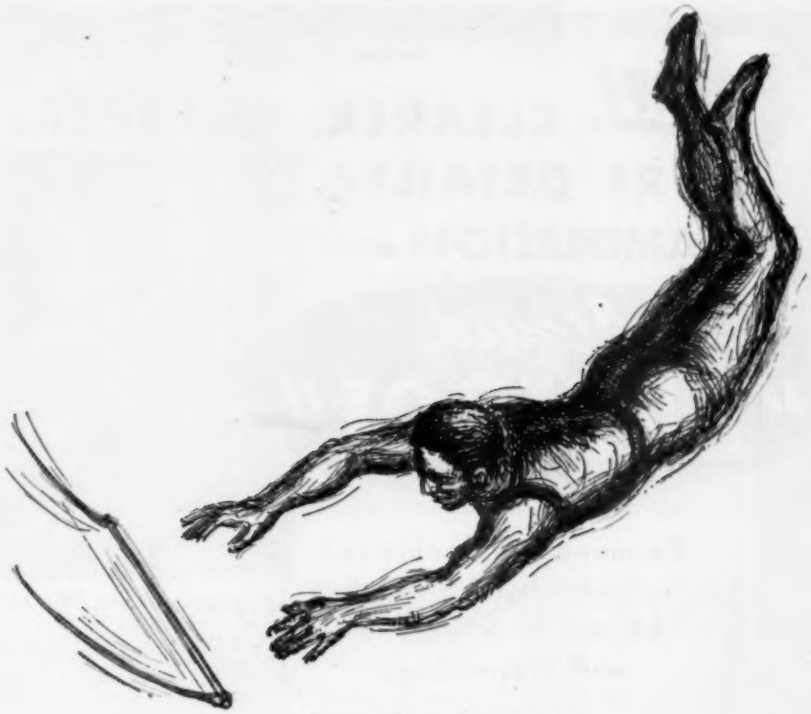

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1. Schaaf, R. S., Hurst, J. W., and Williams, C.: Med. Clin. North America (Mass. Gen. Hosp. No.) p. 1255 (Sept.) 1949

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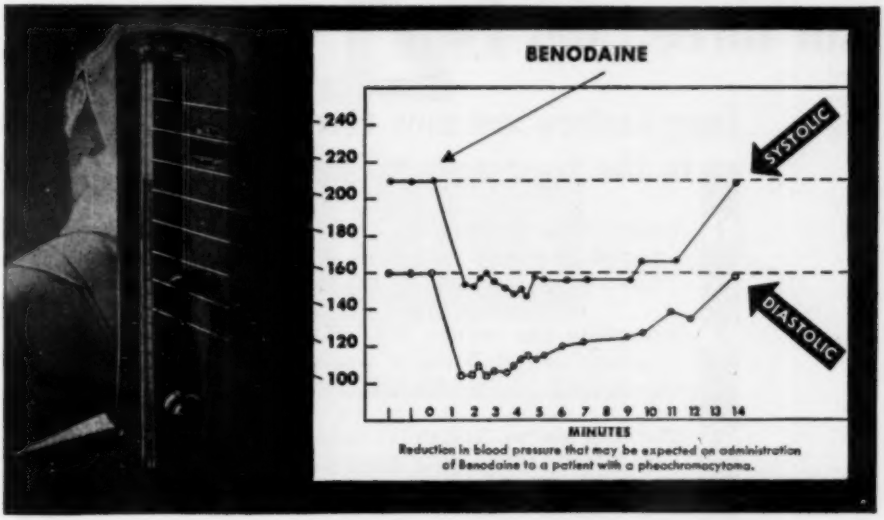
Refs. *Current Medical Digest, June, 1951
*Drs. Windholz, Kaplan, Jones: California Medicine, March, 1951; Radiology, April, 1951



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Complete literature is available on request.

* * *

1. Becker, M.C., Bass, R.D., and Robbins, C.M., *Postgraduate Medicine* 6:408–412, November 1949.
2. Goldenberg, M., and Aranow, H. Jr., *J.A.M.A.* 143:1139, July 29, 1950.
3. Calkins, E., Dana, C.W., and Howard, J.E., *J.A.M.A.* 145: 880, March 24, 1951.

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Merrell
1828

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1. Meyer, K. et al. Am. J. Med. 5:482,1948. 2. Wang, K. J. and Grossman, M. I. Am. J. Phys. 155:476,1948. 3. Grace, W. J. Am. J. Med. Sc. 217:241,1949. 4. Hufford, A. R. Rev. of Gastroenterology. 18:508, 1951.

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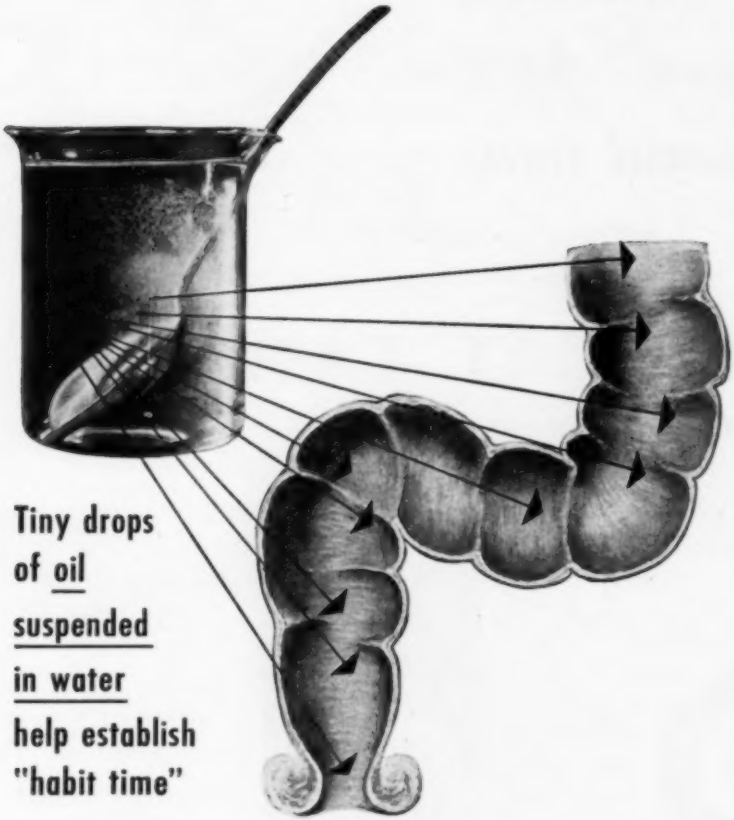

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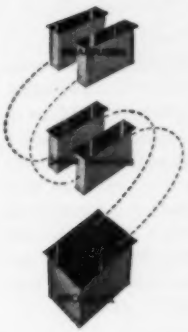

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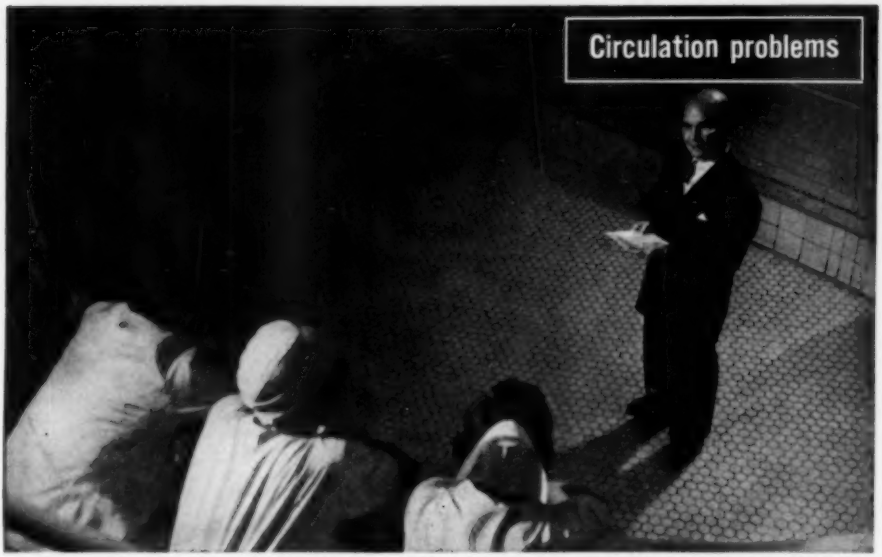

. . . and delay in replenishing the blood fluid makes it difficult to restore the original circulatory volume.

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*Price, P.B., J.A.M.A. *145*:781 (March 17) 1951

Sharp & Dohme, Philadelphia 1, Pa.

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THE REVERSIBILITY OF CERTAIN RHEUMATIC AND NONRHEUMATIC CONDITIONS BY THE USE OF CORTISONE OR OF THE PITUITARY ADRENOCORTICOTROPIC HORMONE *

By PHILIP S. HENCH, M.D., F.A.C.P., *Rochester, Minnesota*

IT may be appropriate to discuss in this Nobel Lecture three general aspects of cortisone and pituitary adrenocorticotropic hormone (ACTH): (1) the development of the theory which eventually led to the use of cortisone and ACTH in rheumatic and certain other conditions; this I shall do in some detail, giving certain data not published heretofore; (2) the present status of cortisone and ACTH in general medicine; this topic I shall discuss summarily in view of the several current reports thereon; and (3) some major requirements for the orderly development of cortisone and ACTH as therapeutic agents; this aspect will be touched upon briefly.

DEVELOPMENT OF THE THEORY WHICH LED TO THE USE OF CORTISONE AND ACTH IN RHEUMATIC DISEASES

Previous Opinions on the Prognosis of Rheumatoid Arthritis. The anatomic and clinical identity of what we now call rheumatoid arthritis was established fairly clearly about 100 years ago. During the next 75 years medical writers emphasized the distressing chronicity of this condition.

Rheumatoid arthritis was called "one of the most intractable, obstinate and crippling diseases that can befall the human body." [184] Distinguished English clinicians were concerned by "the great and lasting feebleness" [104] which the disease produced and by its "cases of ruin and despair, in one sense more malignant than cancer." [280]

A contrasting feature of rheumatoid arthritis, that of its occasional

* Nobel Lecture delivered in Stockholm, December 11, 1950. Received for publication July 9, 1951.
From the Division of Medicine, Mayo Clinic.

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remissions, attracted the attention of some writers.[105, 162, 284] But relatively complete remissions were so uncommon or so unpredictable that they were regarded as medical curiosities, the spontaneous appearance or therapeutic induction of which was hardly to be expected. This air of pessimism regarding the rheumatic diseases in general and rheumatoid arthritis in particular still finds expression in some of the modern writings and texts.

Ameliorating Effect of Jaundice on Rheumatoid Arthritis. It was in this gloomy tradition that, beginning about 1923, I served my rheumatologic apprenticeship. But on April 1, 1929, a 65 year old patient at the Mayo Clinic told me an unusual story. A few days before that date he was painfully affected with rheumatoid arthritis, as he had been for four years. Then jaundice suddenly developed, and within a week most of his arthritic manifestations had disappeared. The jaundice lasted five weeks but the rheumatoid arthritis did not relapse until several weeks after the jaundice had disappeared.

The thought occurred: Instead of being relentlessly progressive, this disease, rheumatoid arthritis, may be potentially reversible, more so than we have believed, perhaps rapidly so.

During the next five years (1929 to 1934), observations were made on 16 patients with chronic arthritis or fibrositis in whom jaundice of different types and degrees developed.[121d, e] If the jaundice was deep enough and was characterized by bilirubinemia of the "direct-reacting type," the rheumatic symptoms quickly diminished or disappeared for varying lengths of time (days to months) and then gradually returned.

Early Speculations Regarding the Ameliorating Agent of Jaundice. The fact that, contrary to general opinion, rheumatoid arthritis was potentially reversible, and rapidly so, thus became increasingly apparent.[121f, g, j, k] But what agent was responsible for the sudden reversibility of this disease during hepatitis with jaundice? At first the dominant feature of visible jaundice suggested that a biliary constituent might be responsible.[121d, e] Was the amelioration of rheumatoid arthritis the result of a temporary excess in the blood and bodily tissues of a normal biliary constituent, such as bilirubin or bile acids, or of an abnormal substance produced during jaundice, such as an autolysate of the liver or of some other tissue?[121d, e] It seemed reasonable to believe that such striking relief from rheumatoid arthritis was effected by some "specific chemical substance"[121b, i] which was normal to the human organism, rather than by an abnormal material.[121f, h] Therefore the hope was expressed "that jaundice provides to the general circulation not an abnormal product but a normal constituent, adequate amounts of which perhaps the arthritic patient did not have."[121f, h] But because the ameliorating effect of jaundice sometimes lasted several weeks after the values for serum bilirubin in blood had returned to normal, it did not seem likely that bile pigments were responsible.[121f, h]

Therapeutic Implications. The therapeutic implications inherent in

these observations were recognized, and the hope was expressed that further studies might lead to the discovery of the responsible agent which might some day be provided at will.[131e, h] "A study of the phenomenon may enhance our knowledge of the pathogenesis of these (rheumatic) diseases and may lead to some superior method of treatment." [131j]

Attempts to Reproduce the Phenomenon of Relief by Using Substances Related to Jaundice and the Liver. A search for the ameliorating agent, "nature's dramatic antidote," [131g] was begun. To test the validity of the conjectures mentioned above, and in an attempt to reproduce the phenomenon of relief which may occur during spontaneous jaundice, various methods were employed.[131g, h, j, k] Volunteers with rheumatoid arthritis were given bile salts by mouth, a derivative of a bile acid (Decholin) orally and intravenously, liver extracts parenterally, ox bile by proctoclysis, and large amounts of human bile by stomach tube. A few other rheumatoid volunteers underwent transfusion with blood from highly jaundiced patients. But these procedures had no significant antirheumatic effect. One rather desperate rheumatoid patient permitted me to give her toluylene diamine by mouth; unfortunately and surprisingly, the jaundice induced thereby was of the hemolytic type and did not induce a remission.[131h] Then, to other volunteers with rheumatoid arthritis, bilirubin was given intravenously alone, or in combination with Decholin, after the method of Thompson and Wyatt.[308] Although the patients experienced marked hyperbilirubinemia and became strikingly pigmented, the results were negative, or at least quite inferior to the effects of spontaneous jaundice.[131g, h]

The ineffectiveness of these various substances, the ones most obviously related to jaundice, strengthened an earlier suspicion that, despite the dominant feature of visible jaundice, the antirheumatic "substance X" [131h] might be "an extrahepatic substance found or activated elsewhere than in the liver as the indirect result of jaundice," [131g, j] or at any rate, that it might be some substance not necessarily related to jaundice. Thus it was stated, "Among other phenomena, pregnancy, which seems to have little or nothing to do with bilirubin, often provokes a similarly effective if less dramatic remission in (rheumatoid) arthritis. . . . If this represents a chemical control, I wonder if nature in the last analysis has more than one way of controlling the arthritic process. There should be some common denominator between the two reactions and, offhand, bilirubin seems to be excluded." [131h]

Ameliorating Effect of Pregnancy. For many years observers, noting the greater incidence of rheumatoid arthritis among women, had speculated as to possible relationships between this disease and the menses, pregnancy and the postpartum state. The literature of the past century contains scattered references to the subject, generally only a sentence here or a paragraph there. Earlier writers generally believed that pregnancy, and especially the puerperal state, exerted an adverse effect on patients with rheumatoid arthritis.[10, 50, 201, 314] But it was also occasionally noted that pregnancy some-

times temporarily checked the disease.[106, 191] In summary, the conflicting and confusing opinions stated that rheumatoid arthritis may be precipitated by or first appear during pregnancy; that it may be aggravated during or relieved partially or completely by pregnancy; or that the disease is unaffected by pregnancy but aggravated by the postpartum state. No critical investigation appears to have been undertaken to clarify these confusions.

At the Mayo Clinic we saw, not infrequently, patients who had become pregnant during the course of their rheumatoid arthritis. It was observed that most of them noted, not long after the onset of pregnancy, an undramatic and slowly progressive development of relief from their arthritic disability. Prior to 1929 this phenomenon did not engage our attention except for the matter of recording it in the appropriate records. But after 1931 records of these cases were more carefully made and assembled by my colleague, Dr. Charles Slocumb, and me, because of my growing belief that this phenomenon of relief was analogous to, if not identical with, that which may occur during jaundice,[131d, f] and that the same agent might be responsible for the relief during both pregnancy and jaundice, although the mechanism for developing the agent might be different.[131k]

Relationship Between the Antirheumatic Agent of Jaundice and That of Pregnancy. As a result of observations on the effect of 34 pregnancies on 20 patients with rheumatoid arthritis, the pattern of the articular relief during pregnancy was described in 1938.[131f] A more extensive study was summarized in 1949.[131m] Regarding a possible relationship between the antirheumatic substance X of jaundice and that of pregnancy, the following tentative conclusion was reached: "It does not seem illogical to suppose that the agents responsible for both these phenomena are closely related, perhaps identical, and if the agent is a chemical substance, it would appear that it is neither bilirubin nor a strictly female sex hormone." [131k, f]

Could Substance X Be a Bisexual Hormone? The comment continued: "It is interesting to note the close chemical relationship between such diverse substances as cholesterol (which may increase in blood in both jaundice and pregnancy), ergosterol, the precursor of vitamin D (which was, in 1938, considered by some to be useful in rheumatoid arthritis), some of the sex hormones (which were occasionally given to rheumatoid patients with negative or equivocal results), cortin and bile acids. Further studies are in progress to discover if possible, the responsible agents for therapeutic purposes. If the potent common denominator of these two phenomena—the ameliorating effects of pregnancy and of jaundice—can be discovered, progress in treatment may be expected." [131f]

One of the chief biologic changes related to pregnancy was known to be a marked increase in the bodily concentration of certain hormones. Thus it was the studies on the ameliorating effect of pregnancy which led to a transfer of interest from some biliary substance to a consideration of some hormone as the possible substance X. Although cortin (whole adrenal

extract) was one of the glandular extracts which we listed for consideration in 1938, we did not use it until later.

But which (if any) hormone might substance X be? Despite the dominant feature of pregnancy, the following facts seemed to speak against the likelihood that the unknown antirheumatic agent was a unisexual hormone, that is, a female hormone or one strictly related to pregnancy: (1) Jaundiced rheumatoid males obtained the same relief as nonjaundiced pregnant females. (2) The pattern of relief during pregnancy did not clearly coincide with the time periods during which any one of the then known female sex hormones was reported to be increased. (3) Certain female sex hormones, administered from time to time to a few rheumatoid patients by various workers, including my colleague, Dr. Charles Slocumb, had produced no striking or consistent relief. Hence it was conjectured that, if substance X was a hormone, it was not a unisexual (female) hormone but a bisexual one.[131d]

Specificity of These Phenomena. Changing views were held as to the specificity of the effects of jaundice and pregnancy. Among our first patients relieved by jaundice or pregnancy were a few with fibrositis, intermittent hydrarthrosis, or sometimes sciatica, as well as those with rheumatoid arthritis. Therefore the phenomenon of relief was at first (1934) regarded as "probably nonspecific," at least not specific for rheumatoid arthritis alone.[131e, f]

Later (1938), the phenomenon was tentatively regarded as being "relatively specific for rheumatoid arthritis and fibrositis." [131h, j] Then (1940) it was noted that patients with hay fever and severe asthma, egg sensitivity or migraine were sometimes relieved by intercurrent jaundice; in other words, hepatitis with jaundice appeared to "invoke an anti-allergic as well as an antirheumatic reaction." [131l] Finally, data were collected which suggested that patients with psoriasis or psoriatic arthritis, asthma, migraine, hay fever, Addison's disease and myasthenia gravis were sometimes relieved during pregnancy and/or jaundice.[131m] Therefore the phenomenon of relief by the hypothetical common denominator of jaundice and pregnancy came to be regarded as "group-specific rather than disease-specific." [131k, m] This of course enhanced greatly the potential importance of substance X.

Related Phenomena. Through the years during which these studies on the effects of jaundice and pregnancy on several diseases, but particularly on rheumatoid arthritis, were being pursued, it was noted that somewhat similar, though less dramatic, symptomatic remissions could be induced occasionally by reactions to typhoid vaccine,[131a, k, m] not infrequently by almost any surgical operation,[131d, k, m] and also by short periods of starvation.[131k, m] We suspected that anesthesia alone might be an important factor in the production of the transient postoperative relief which followed diverse surgical procedures on patients with rheumatoid arthritis.[131d, m] My colleague, Dr. Slocumb, confirmed this fact, producing certain degrees of

articular improvement by giving various anesthetic agents alone to several rheumatoid volunteers.[131m]

The phenomena of relief by these various other procedures were regarded as probably related somehow to the more familiar phenomena induced by jaundice or pregnancy.[131d, f, k] But for a long time speculations thereon did not provide a clue as to the probable identity of substance X.

Recapitulation of Conclusions and Conjectures (1929–1940). In summary, the following conclusions and conjectures were arrived at from 1929 to 1940, partly as a result of various clinical observations and partly as the result of numerous experimental failures.* In passing, it may be worth mentioning that the development of the theory which eventually led us to the use of cortisone and ACTH in rheumatic and other conditions was guided as much by our failures to induce experimental remissions with certain particular substances as it was by interrelating the clinical observations.

It was decided that (1) rheumatoid arthritis was not necessarily a relentless progressive disease but was potentially reversible; (2) there developed during jaundice and pregnancy (perhaps also during typhoid vaccine reactions, starvation and anesthesia) an antirheumatic "substance X"; (3) if nonjaundiced pregnant women and jaundiced males were relieved in a similar manner, as seemed likely, substance X was not a unisexual (female) hormone nor the product of a damaged liver; (4) substance X was probably a specific chemical substance [131h, i] or a biologic compound [131j, m] which is normal to the human organism,[131f, h] one which is specific in nature and function; [131h, m] and (5) in view of the ameliorating effect of both pregnancy and jaundice, substance X might be a bisexual hormone.

Could Substance X Be an Adrenal Hormone? Prior to 1938, my conferences with Dr. Kendall concerning the possible nature of substance X were irregular, infrequent and casual. But thereafter he became my chief collaborator, and my conferences with him became more and more frequent. As we tried, on innumerable occasions from 1938 to 1948, to conjecture what might be the chemical nature of substance X, neither of us knew that he and his associates, working on compound E (the adrenal cortical substance, 17-hydroxy-11-dehydrocorticosterone) in his laboratory a few yards away, were at that very moment isolating, identifying and preparing to synthesize "substance X" or a reasonable facsimile thereof.†

It would not be proper to infer that my confidence in the validity of these developing concepts was constant and unwavering. One was often dealing

* During the several early years (1929 to 1940) in which the abovementioned clinical observations were made and these ideas were being formulated, I had the counsel and aid of many colleagues at the Mayo Clinic, chief of whom were my departmental colleague, Charles H. Slocumb, M.D., who became associated with me in 1935, and Edward C. Kendall, Ph.D., of the Department of Biochemistry.

† It is the privilege of Dr. Kendall and Dr. Reichstein to describe on this occasion, in their own Nobel lectures, the isolation, identification and production of the substance which was called compound E by Kendall, substance Fa by Reichstein and his associates, and compound F by Wintersteiner and Pfiffner.

only with subtle suggestions, and it was frankly recognized that one or more of the main presumptions were not based on certain knowledge or facts, but were the (seemingly) logical development of some other presumption which, however reasonable it might appear to be, might be erroneous. Hence, other possibilities were entertained from time to time and occasional excursions into the empiric were indulged in. In 1938 Dr. Slocumb and I gave to a few patients with rheumatoid arthritis adrenal lecithin prepared for us by E. C. Kendall and B. F. McKenzie. We administered it, not as an adrenal product per se, but in an attempt to produce hyperlipemia which often accompanies jaundice or pregnancy. No significant relief resulted.

Decision to Administer Compound E of Kendall. During one of our conferences in January, 1941, Dr. Kendall and I decided to administer to rheumatoid patients the adrenal cortical substance, 17-hydroxy-11-dehydrocorticosterone, whenever it might become available. The reasoning behind this joint decision was fragile, but it was logical in the light of what we knew then and know now. Sixteen years previously, in 1925, the weakness, fatigue and low blood pressure common among patients with rheumatoid arthritis, which we then called "chronic infectious arthritis," suggested to me that in connection with, or in addition to, a supposed factor of infection, secondary metabolic changes were present, and that the adrenal glands might somehow be involved in this disease.[121b, c] But the postmortem examination,[121c] in 1925, of the adrenal glands of two patients with rheumatoid arthritis lent no support to the vague suspicion regarding an adrenal factor, and the notion, though not forgotten, was laid aside.

In our conference of January, 1941, Dr. Kendall (with whom I had previously discussed not only the abovementioned vague notion of an adrenal factor in rheumatoid arthritis but also the striking if transient remissions sometimes induced by reactions to typhoid vaccine) remarked that his compound E increased the resistance of animals against reactions to typhoid vaccine. Kendall's compound E [170–172, 209–212] (compound Fa of Reichstein) [253, 254] was being separated in small amounts from the adrenal glands of animals but had not yet been tested in any human disease. Might it be useful against rheumatoid arthritis? The decision to try it out was recorded in my pocket notebook. But we did not know then that almost eight years would elapse before there would be enough of this adrenocortical substance to administer to a rheumatoid patient. Our plan to use it remained attractive through the several years of waiting.

In lieu of this hormone, Slocumb and I, in 1941, gave Kendall's adrenal cortex extract, "cortin," to three patients with rheumatoid arthritis, without impressive results.[134] With none of Kendall's compound E or any other likely product available to us, we then (1941 and 1942; 1946 to 1948) produced in a few arthritic volunteers jaundice induced by the oral use of lactophenin after the method of Hanssen.[121] Temporary remissions were induced but we could not identify the responsible agent.[121m]

First Use of Kendall's Compound E in Rheumatoid Arthritis. In August, 1948, we tried to relieve a woman badly crippled with rheumatoid arthritis by giving lactophenin orally to induce jaundice. But no jaundice developed. We then decided to try compound E (Kendall) if it was available. Our earlier conjecture that substance X might be an adrenal hormone had meanwhile become strengthened by the observations of others that some of the seemingly diverse agents which often temporarily relieved arthritic patients (foreign protein reactions, starvation, various surgical operations) were now known to be capable of stimulating the adrenal cortex.[37, 38, 93, 303, 306, 318–320, 324, 325] But despite our sustained desire to use this hormone whenever it might be available, we had no firm conviction, only the hope, that this compound might be substance X.

A letter [131] requesting enough of Kendall's compound E for one patient was sent on September 4, 1948, to Merck & Co., Inc., whose research chemists (chiefly Dr. L. H. Sarett),[265, 266] working in collaboration with Dr. Kendall and his associates,[170–172, 209–212] had finally succeeded in making a small amount of this substance. The letter concluded: "We know that there is a potentially provokable mechanism (for the reversibility of rheumatoid arthritis) which is activated by pregnancy and jaundice very rapidly, by jaundice for example within three days. . . . Therefore if any adrenal compound is of real significance in rheumatoid arthritis we would expect to see some results within a very few days." A small supply of Kendall's compound E was soon received from Dr. Randolph Major, vice president, and Dr. James Carlisle, medical director of Merck & Co., Inc.

Dr. Kendall and I decided to use for this first rheumatoid patient daily doses of 100 mg. intramuscularly, so that we might not commit the error of underdosage. Thus, on September 21, 1948, Dr. Slocumb began to administer to the abovementioned patient daily doses of 100 mg. of compound E (not the acetate) in the form of a crystalline suspension in saline solution. Within three days the patient was markedly improved and continued to improve until the daily dose was reduced to 25 mg.

Because of very limited supplies and the difficulties which were encountered in the preparation of the early suspensions, only four more patients were given compound E (which Dr. Kendall and I later renamed "cortisone") from September, 1948, to January, 1949. The preparation of the suspensions of compound E for intramuscular injection presented many problems which, step by step during these months, were solved by Dr. Kendall, who has discussed them elsewhere.[170–172]

In January, 1949, we requested a supply of ACTH from Dr. John R. Mote, then director of laboratories, Armour and Company. We first administered it on February 8, 1949, to a patient with rheumatoid arthritis. Thereafter cortisone (Merck) or ACTH (Armour) or both were given by my associates, Dr. Slocumb and Dr. Polley, and by our assistants to a series of patients with severe or moderately severe rheumatoid arthritis. The first

report of results was presented April 20, 1949, by Hench, Kendall, Slocumb and Polley.[132] Dr. Randall Sprague had become our advisor in metabolic procedures and carried out the metabolic studies which were made in some of our cases by himself in collaboration with Dr. Power, Dr. Mason, Dr. Albert and Dr. Mathieson.[293]

The Present Status of Cortisone and ACTH in General Medicine

General Results of Cortisone or ACTH in Rheumatoid Arthritis. Clinical Effects: To date several thousand patients with rheumatoid arthritis in various parts of the world have received either cortisone (generally cortisone acetate), or ACTH daily for periods varying from only a few days to many months. The results reported from the Mayo Clinic[131a, c, 132-137, 273] have been confirmed by other workers.[3, 9, 15, 16, 25, 26, 32, 38, 53, 56, 59, 60, 78, 82, 84, 85, 99, 110, 111, 147, 151, 153, 163-165, 181, 190, 194, 197, 199, 204, 220, 235, 248, 262, 263, 281, 282, 284, 286, 287, 299, 310, 311, 317, 321]

In practically all cases, most of the symptoms have markedly and quickly diminished during the use of either hormone. Because the clinical results from ACTH are essentially similar to those from cortisone, it is assumed that ACTH, when injected intramuscularly, stimulates patients with responsive adrenals to increase the production of their own cortisone, or a similar steroid hormone such as 17-hydroxycorticosterone (Kendall's compound F).*

When either hormone is given there is a diminution, first of the subjective phenomena (stiffness, soreness, tenderness), later of the objective features (fever if present, swelling, flexion contractures if not too long established, size of rheumatoid nodules and enlarged lymph nodes). A sense of well-being, increased psychomotor activity, and increased appetite and weight commonly develop.

Laboratory abnormalities tend to diminish. Sedimentation rates generally decrease, often rapidly. Hemoglobin concentrations may increase,[126, 132, 134] and hyperglobulinemia usually decreases. Urinary 17-ketosteroids generally diminish during the daily use of 100 mg. doses of cortisone, increase during the use of ACTH.[134, 206, 291, 293] Either hormone increases the excretion of corticosteroids in urine. Urinary amino acids increase during remissions induced by cortisone or ACTH as they do during spontaneous remissions or those related to pregnancy or jaundice.[24, 148-150, 159, 297] The hormones may alter the alpha waves in electroencephalograms.[25, 145, 248] They do not prevent formation of antibodies, or alter agglutinins to sensitized sheep erythrocytes present in sera of rheumatoid patients.[302]

Subjective relief may be marked but incomplete, almost complete or complete. Objective features usually do not disappear entirely: some fusiform thickening or painless articular bogginess may remain to show that the disease is suppressed rather than cured. Residual architectural damage

* This has since been named "hydrocortisone."

to cartilage and bone remains unaffected. Articular biopsies of synovia, carried out before and at various times during the use of these hormones, have revealed varying degrees of improvement.[15, 134]

Results of Hormonal Discontinuance: Relief of symptoms has usually lasted as long as the hormones were given. But thereafter relapses have generally occurred, usually within one or two months, occasionally more promptly and severely (rebound relapses).[134] But a number of patients have retained much, sometimes almost all, of their relief for several months without the aid of the hormones.[9, 134, 199, 235, 273] A few other patients have experienced a short relapse for about a month, then regained much of their previous improvement.[134, 151] The question arises whether these posthormonal remissions were spontaneous and coincidental or induced by the previous hormonal usage.

Undesirable Physiologic Effects ("Side Effects") of Cortisone and ACTH: The doses of hormones required to suppress rheumatoid arthritis are relatively high compared to doses which protect addisonian patients (or patients with adrenal insufficiency).* Often these doses are well tolerated, especially if given for only a few weeks; sometimes they are not, in which case the consequences of hypercortisonism develop, and any one or more of a variety of effects may occur. Some of these are of little importance; others are of greater consequence and may provide certain hazards to certain patients.[25–27, 48, 99, 132–137, 149, 220, 248, 262, 291, 293, 311]

Side effects encountered fairly frequently have been mild irritability with increased psychomotor activity; an initial retention, generally mild, of sodium chloride and water, producing fluctuant weight with or without visible pretibial edema; mild hypertrichosis; acneiform eruption or rounding of the face.[19, 134, 273, 293] Fluid retention, if it develops, is usually mild, generally lasts only a few days and may then disappear even though the dosage of hormone is not altered. The doses currently employed do not as a rule produce deficits of electrolytes or nitrogen, at least in persons allowed to eat at will. Certain rare or rather rare side effects are of special interest: transient renal glycosuria[55, 153, 168] or transient significant reduction of carbohydrate tolerance;[25, 36, 54, 55, 156, 157, 195, 223, 242, 292, 293] hypopotassemic hypochloremic alkalosis;[134, 291, 293] transient major alterations of psyche,[132, 134, 145, 195, 258] which may develop for a few days generally in persons with markedly disturbed personality patterns, or with prepsychotic or psychotic dispositions; spontaneous fractures occurring in elderly osteoporotic persons, usually after excessive physical activity,[24b, 114] and thrombophlebitis or vascular occlusion.[112, 225, 296] Significant interference with wound healing has occurred rarely in patients receiving the usual doses employed.[24b, 63, 155, 248, 278, 279] So far, all the side effects observed by us and others have been reversible and have dis-

* During the past few months we have been using smaller suppressive and smaller maintenance doses than we used previously; results have been generally quite satisfactory and will be reported elsewhere.

appeared when the dosage was lowered sufficiently, or the use of the hormone discontinued.

The side effects have been listed and discussed in detail elsewhere.[134, 137, 273, 293] Physicians who would use these hormones should become familiar with these possible side effects and with certain measures devised for their prevention, modification or control.

Because of their potential effects, cortisone or ACTH should be used with caution in the following: hypertensive cardiovascular disease,[48, 227, 241, 242] diabetes mellitus, tuberculosis, old rheumatic carditis with decompensation,[216, 217, 220, 311] latent or frank psychoses,[258] marked osteoporosis associated with senility or with rheumatoid arthritis,[311] peptic ulcers,[18, 69, 119, 181, 264] glomerulonephritis [41, 169] and possibly active syphilis.[218]

Certain measures have been devised to prevent or modify some of the undesirable effects.[134, 137, 293] These include limitation of sodium chloride intake to 1 gm. or less, and, if necessary, the oral use of a diuretic, such as potassium nitrate, to control retention of fluid; oral use of potassium chloride if necessary to control deficits of potassium and chloride; personality appraisals and the avoidance or cautious use of the hormones in patients with prepsychotic tendencies;[258] early reduction of the initial suppressive doses to lower "maintenance doses" in all cases in which use of the hormones is prolonged,[26, 27, 99, 137, 323] and use of estrogen (such as 5 mg. of estrone twice weekly) in menopausal women somewhat intolerant of cortisone.[134]

The incidence of troublesome side effects has been fairly low among patients given the hormones for a few days or weeks. As a result of the use of the procedures just mentioned and others, the incidence of side effects has been declining among patients given the hormones for many weeks or months.

Potentiation of Cortisone and ACTH: Attempts have been made to find some synergistic material which, when given with cortisone or ACTH, would enhance the effect of doses of cortisone or ACTH which were too small to produce side effects. Salicylates and vitamin C, and more recently insulin,[139, 140, 304] have been recommended. So far we have seen no potentiation of cortisone from such measures. The concomitant use of para-aminobenzoic acid has been recommended.[329] The effects of cortisone or ACTH given in conjunction with gold salts to patients with rheumatoid arthritis are being investigated; detailed results have not been reported.[101, 112, 147, 148, 201]

Gaps in Our Current Knowledge of Basic Facts. A completely rational and physiologic method for the administration of these hormones cannot yet be developed because we presently lack sufficient knowledge concerning certain basic facts. The main defects in our knowledge can be summarized briefly: 1. It is not yet known how much cortisone or ACTH is produced daily by the adrenal and pituitary glands of normal persons, or by patients with rheumatoid arthritis or with one of the other diseases influenced by these hormones. 2. Exogenous ACTH stimulates responsive adrenals to

increase their production of endogenous cortisone, but we do not know how much that increase is in any given case. 3. The administration of exogenous cortisone exerts a suppressive effect on the production of endogenous cortisone, but we cannot yet measure with any degree of precision the decrease in production, which, incidentally, may vary considerably during the administration of the exogenous cortisone. 4. We do not yet know whether cortisone (or hydrocortisone: compound F) is the only adrenal cortical hormone.[206, 207, 228] 5. Little is known about the metabolism of cortisone, about how much is utilized normally by the cells of the body, or how much is (normally) altered or destroyed in the body or excreted before it has had an effect.

Until we acquire some of this knowledge we can only attempt to develop, with intelligence and with concern for calculated risks, an empiric and reasonably safe method of administration.

Optimal Method of Administration of Cortisone and ACTH. For the investigative management of rheumatoid arthritis and other chronic conditions which seem now to require prolonged use of the hormones, the basic policy must be to provide the greatest symptomatic relief that is possible consistent with the avoidance of undesirable physiologic effects. If doses which are needed for full symptomatic relief produce significant side effects, one should reduce the dose and be content with less than full suppression of rheumatic symptoms, at least until a superior plan of administration is developed.

The optimal dosage and method of administration remain to be determined. Various plans of administration of cortisone and ACTH are under investigation.[26, 27, 99, 137, 235] The advantages and disadvantages of each plan have been described.[137] The main schemes include (1) repeated, fairly short, interrupted courses using the same hormone for each course; (2) repeated, fairly short, interrupted courses, alternating the hormones; using, for example, cortisone for the first course, ACTH for the second course, cortisone for the third, and so forth; (3) more or less continued administration of either hormone: first the use of suppressive doses, then a gradual reduction to the level of an effective maintenance dose, and then the prolonged use of maintenance doses given either three days each week (intramuscularly) or daily (orally or intramuscularly). A significant number of rheumatoid patients are being satisfactorily managed by this latter method.[26, 27, 99, 323] The combined use of cortisone and ACTH, given in differing proportions and by differing schedules, is also under investigation.

Oral Administration of Cortisone. The former remarks about cortisone refer chiefly to its intramuscular administration. Current investigations indicate that cortisone is also effective when given orally in tablet form. In May, 1949, one of our rheumatoid patients responded very well to the oral administration of capsules of highly concentrated adrenal cortex extract (Upjohn) containing compounds E and F.[134, 244] From this experience

and from the observations of Heilman and Kendall,[128] who administered cortisone to animals, we concluded that the oral use of cortisone would be effective. Satisfactory results from cortisone tablets given to rheumatoid patients have been reported by Freyberg and his associates,[101, 102] by Kuzell and Schaffarzick,[182] and by Boland and Headley.[27] Our own results have also been satisfactory;[121p, 135, 137] details regarding 100 cases will be reported soon with my colleagues, Ward, Slocumb, Polley and Lowman.[228] The total daily oral dose which is effective in most cases approximates in amount the effective daily intramuscular dose. It is the preliminary impression of Freyberg and his associates, of Boland and Headley and of ourselves that when small doses are given orally several times a day the clinical effect may be more satisfactory and the incidence of undesired effects may be lower than when one large daily dose is given intramuscularly. The new method may be more physiologic, approximating the more or less continuous output of small amounts of cortisone-like material from the human adrenal cortex.

Extension of the Use of These Hormones Against Other Conditions. When the effectiveness of cortisone and ACTH against rheumatoid arthritis became apparent, we remembered that the ameliorating effect of jaundice and pregnancy is not disease specific but group specific.[121k, m] We remembered also that jaundice and pregnancy appear to exert an antiallergic, as well as an antirheumatic, effect.[121k] Therefore it seemed logical to hope that these hormones would be found useful against certain nonrheumatic as well as other rheumatic diseases. If one could assume that cortisone (or a cortisone-like substance such as Kendall's compound F) is the ameliorating agent operating in jaundice or pregnancy, cortisone and ACTH might be expected to be effective against (1) various diseases commonly relieved by jaundice or pregnancy;[121m] (2) diseases which involved essentially the same histologic types of tissues (muscular, fibrous, collagenous) which are affected in rheumatoid arthritis, and (3) certain allergic conditions.[121k, m]

For these reasons, therefore, the first extension of the use of these hormones by us, and then by others, was to cases of lupus erythematosus disseminatus, and acute rheumatic fever, then to various allergic conditions.

Results in Rheumatic Fever: Following the use of either hormone, the acute manifestations of rheumatic fever have generally subsided quickly, some of them (fever, polyarthritis, tachycardia, "toxemia") usually within a few days, others usually within two to three weeks (increased sedimentation rates, augmented P–R intervals, hyperglobulinemia).[1, 11, 12, 20, 133, 134, 188, 213–217, 219–221, 235, 810, 211, 222] When present, preëxisting chronic valvular damage and old cardiac hypertrophy have remained unchanged. But in some cases, certain manifestations of acute carditis have been promptly lessened or abolished, and within the limits of our short follow-up studies (average, a few months) no definite persisting signs of new or increased old carditis have developed from the acute attacks which were suppressed by the hormones.

In a few reported cases in which there was frank or impending cardiac decompensation, use of the hormones has caused troublesome but generally transient retention of fluid. But in most patients with acute rheumatic fever and acute carditis, few if any major side effects have developed.

Cortisone and ACTH, although they suppress symptoms, do not "cure" rheumatic fever, nor is it yet certain that they shorten the inherent duration of its acute phase. Hence they must be given until the natural duration of the acute phase, generally six to 12 weeks, has run its course. Otherwise, as pointed out by my colleagues, Dr. A. R. Barnes and Dr. H. L. Smith, some or all of the acute manifestations will reappear and remain either until the hormone is given again or until the acute phase has spent itself.

Some evidence suggests that the proliferative as well as the exudative manifestations of acute rheumatic carditis may be suppressed by these hormones. If so, their proper use may prevent much pathologic change in the heart. But prolonged observations will be required to determine whether or to what extent these hormones will prevent the initial development or aggravation of rheumatic carditis.

Results in Other Conditions: The acute articular manifestations of gout [14, 24a, 86, 118, 130, 181, 202, 220, 256, 282, 305, 310, 330–332] and the articular complications of disseminated lupus erythematosus,[6, 7, 29, 39, 40, 45, 70, 84, 91, 118, 125, 182, 184, 185, 196, 220, 235, 243, 248, 269, 275, 310, 311, 327] ulcerative colitis,[72, 79, 80, 116, 177, 235, 246] psoriasis [85, 99, 220, 230, 231, 245, 284, 285, 311] and tuberculosis [129, 134] have been found responsive to these hormones in most but not in all cases. Symptoms of osteoarthritis have been modified in some cases but not in others.[14, 17, 24a, 66, 96, 134, 181, 296]

The hormonal effects on the nonarticular features of these diseases have been varied. Many features of disseminated lupus erythematosus have been temporarily suppressed, others have not. Although remissions, not cures, have been induced, use of the hormones has apparently been a "lifesaving measure" in certain acute crises of this disease.[6, 70, 134] In ulcerative colitis, symptomatic relief of intestinal symptoms has been provided more often than objective improvement. In psoriasis, articular lesions have been more responsive than the lesions of skin. In tuberculosis, cortisone and ACTH appear to control hyperergic tissue reactions, and may reduce certain symptoms.[97, 124, 129, 134, 211, 213, 234] But the hormones exert no bactericidal or bacteriostatic effect, and because they inhibit formation of fibroblasts it has been suggested that they may foster the spread of active tuberculous lesions.[53, 73, 81, 122, 167, 224, 235, 278, 279, 311] Therefore they should be used with considerable caution in tuberculous infections (except perhaps for cortisone given locally for ocular lesions), at least for the present. But cortisone does not produce lysis of already existing granulation tissue.[279]

Several types of allergic reactions have been suppressed during the use of these hormones, and sometimes for varying lengths of time thereafter: ragweed hay fever,[49, 134, 249, 251] bronchial asthma [23, 30, 33, 47, 49, 84, 94, 144, 184, 186,

[218, 235, 249–251, 260, 261] status asthmaticus,[311] infantile atopic eczema,[146, 166, 251] urticaria, and certain skin and other reactions due to penicillin,[29, 30, 46, 154] gold,[147, 148] atropine,[46, 154] iodine,[29, 46] aspirin,[46] sulfonamides [46] and other drugs.[46]

One of the more promising fields of usefulness for these hormones appears to be the acute and subacute inflammatory diseases of the eye: uveitis, scleritis, iridocyclitis, keratitis, chorioretinitis, sympathetic ophthalmia and vernal conjunctivitis.[109, 141, 142, 146, 154, 200, 232, 295] In some cases, cortisone in eye drops or ophthalmic ointment has been effective; [124, 146, 259, 285, 295, 324] in other cases, subconjunctival injections were employed.[150, 259]

Less striking, but still of considerable interest, have been the results in cranial arteritis,[271, 272] periarteritis nodosa,[9, 45, 108, 235, 261, 271, 272] dermatomyositis,[84, 220, 233, 267, 287, 311] certain cases of nephrosis,[13, 59, 89, 90, 98, 169, 192, 235, 255] sprue, burns,[61, 62, 328] and certain blood dyscrasias, especially leukemia,[44, 68, 74, 76, 83, 86, 235, 238–240, 268, 288, 299] acquired hemolytic anemia [67, 103] and idiopathic thrombocytopenic purpura.[257]

The possible influence of these hormones on many other conditions is being investigated,[48, 227, 311] and optimistic preliminary reports concerning some of them have appeared. But it will take years to evaluate the results critically. If one confines his attention to those diseases about which opinion seems to be fairly unanimous after one or two years of experience, one finds that about 15 or 20 diseases can be modified markedly or suppressed almost completely, at least temporarily. What makes this the more interesting is that most of these responsive diseases have been heretofore peculiarly resistant to control or even to temporary modification by any previous remedy.

Speculations on the Mode of Action. Many of the numerous physiologic effects of cortisone and ACTH appear to be nonspecific, meaning that if large enough doses are given long enough these effects will develop in anyone, normal or diseased. But the ability of these hormones to ameliorate markedly almost the whole symptom complex of certain diseases appears to be group specific; at least the outstanding clinical results occur in the rheumatic, allergic and collagen diseases.[131n]

But how these hormones accomplish, for example, their antirheumatic effect is still quite unknown.[86, 131n, o, 137, 158, 195, 235, 248, 311] Because rheumatoid arthritis infrequently complicates Addison's disease, and because the daily dose required to suppress the responsive inflammation is considerably greater than that required by addisonian patients, it appears that the hormones do not merely correct some simple deficiency, such as one from an inadequate production of cortisone or ACTH. The administration of cortisone may correct a relative, not an absolute, deficiency, and satisfy an increased tissue requirement for the hormone.[137] Thus, current opinion is that the hormones act at the tissue, or cell, level. But this tentative conclusion must be the subject of much further study.

In providing relief, these hormones do not kill germs or appear to remove the unknown etiologic irritants of the conditions which they ameliorate. Thus they do not "cure" the diseases the symptoms of which they modify so profoundly. But in an unknown manner they provide the susceptible tissues with a shieldlike buffer or protection against a wide variety of irritants.

The hormones influence beneficially, not the irreversible pathologic anatomy or ashes of disease, but the reversible part of the responsive diseases, their pathologic physiology, that is, the reaction of tissues to the irritant.

To use a figure of speech, these hormones appear not to extinguish the fire or to act like a carpenter to repair the damage of the fire. Instead, they appear to "dampen the fire," or to provide, as it were, an asbestos suit behind which the patient, like some Biblical Shadrach, Meshach or Abednego, protects his tissues from the fire. If this protection is removed prematurely, before the fire has spent itself, the patient and his tissues will react again to the burning. But if the protection is not discarded until the natural duration of the fire is over, the patient remains largely free of symptoms and apparently "well."

Search for Substitutes for Cortisone and ACTH. Miscellaneous Steroids: Because of the cost, limited supplies and potential side effects of cortisone and ACTH, some effective steroidal substitute has been intensively sought. So far the search has been fruitless. About 50 steroids have been tested by us and others for antirheumatic and other properties: 11-dehydrocorticosterone (Kendall's compound A),[134, 244] 11-desoxycortisone (substance S of Reichstein),[99, 244, 262, 263, 281, 307] progesterone or 17-hydroxyprogesterone,[2, 22, 56, 82, 99, 173, 174, 179, 183, 229, 244, 252, 262, 263, 283, 307] pregnenolone (delta-5-pregnenolone or 21-acetoxypregnenolone),[56, 71, 92, 95, 96, 99, 117, 151, 160, 179, 229, 244, 263, 270, 274, 289, 300] testosterone,[32, 82, 92, 99, 117, 160, 174, 229, 274, 289] desoxycorticosterone acetate, sometimes alone but generally with ascorbic acid,[21, 42, 57, 65, 77, 82, 115, 123, 161, 173, 174, 178, 186, 187, 229, 244, 262, 263, 283, 286, 287, 289] and other steroids.[48, 50, 99, 173, 174, 183, 229, 244, 262, 263, 281, 283, 284, 307] With the exception of 17-hydroxycorticosterone (Kendall's compound F, substance M of Reichstein), none has given significant results in the limited range of doses thus far explored. But a comparative study, by Polley and Mason,[244] of the chemical configurations of these ineffective steroids with those of the potent compounds E and F has revealed the structural requirements which appear to give the steroid nucleus its antirheumatic properties and to be responsible for the physiologic activity of cortisone. These are a ketone group at carbon-3, either a ketone or a hydroxyl group at carbon-11, a ketone group at carbon-20, a hydroxyl group at carbon-17 and at carbon-21, and a double bond between carbon atoms 4 and 5.

Compound F (Kendall): Certain data suggest that Kendall's compound F (17-hydroxycorticosterone: hydrocortisone) may be the ultimate product

of the adrenal cortex.[206, 207, 228] Although our supplies of compound F have been very meager, the antirheumatic activity of this compound appears to be comparable to that of cortisone.[135, 137, 244]

Summary of Present Status. Depending on the amount of their experience with these hormones, and also upon their own aggressiveness or conservatism, American physicians, including clinical investigators, would express widely differing opinions as to the present status of these hormones in general medicine. Until recently the hormones were used at the Mayo Clinic, not particularly as forms of treatment, but as tools for physiologic investigations. But physicians cannot remain academic and aloof to the army of patients who ask, "How soon can you treat me with these substances safely and within my means?"

Many investigators with one or two years of experience in the use of these hormones believe that cortisone and ACTH can now be given limited practical application in the management of conditions which may require relatively short-term usage for a few days or weeks, for example, acute gouty arthritis, acute rheumatic fever, acute ocular inflammations, acute or seasonal allergies, acute skin sensitivities, and acute crises of disseminated lupus erythematosus.

As for the application of cortisone and ACTH to the management of responsive chronic diseases, the many investigations now being made are revealing the scope and limits of their usefulness. Certain conservative, critical rheumatologists have already expressed their belief that the careful use of these hormones as therapeutic agents for rheumatoid arthritis is justified and appears properly to be impending.[26, 28, 60, 100]

To permit the appropriate therapeutic and investigative use of these hormones, the United States Food and Drug Administration has released them for sale to all licensed American physicians.

Requirements for the Orderly Development of Cortisone and ACTH as Therapeutic Agents

For the proper and orderly development of cortisone (or the cortisone-like compound F) and ACTH as therapeutic agents, chemists must learn how to make these materials in more or less unlimited quantities, and physiologists and physicians must try to learn how they produce their beneficial effects, or, in lieu of such basic knowledge, physicians must learn how to use them empirically but nevertheless intelligently and safely. As stated elsewhere, "In the presence of functioning adrenal glands we must learn how to coöperate with them rather than to try to dominate them or take over their functions." [135]

Problems of Production. In the competition for the attainment of their respective goals, the biochemist and chemical manufacturer are somewhat ahead of the physiologist and the clinical investigator. Despite enormous

difficulties, the production of these hormones, especially cortisone, has been greatly increased.

Cortisone: Although none of the 36 steps required to convert desoxycholic acid into cortisone has been by-passed, some of the steps have been made less costly, less time-consuming, and productive of greater yields;[51] hence, the cost has fallen from an estimated production cost of $1,000 a gram in 1948 to the current (November, 1950) sales price of $35.00 per gram.* Despite certain news reports, cortisone has not yet been made from strophanthus plants,[43, 316] soybeans or Mexican yams.[203] But the search for new starting materials for the partial synthesis of cortisone, and for methods for its total synthesis, continues and will doubtless be successful in time.

ACTH: The pituitary glands of animals (beef, horses) other than the pig now yield significant amounts of potent adrenocorticotropic hormone (Armour's ACTH; Wilson's corticotropin). Potent ACTH is also being made from the pituitaries of whales by Scandinavian scientists.[143]

A "long-acting" preparation of ACTH, prepared by Armour and Co., has given satisfactory results in a few cases of rheumatoid, gouty and psoriatic arthritis, rheumatic fever and ulcerative colitis. Maximal duration of activity was 48 hours.[223]

Several investigators have suggested that peptide fragments of ACTH may retain physiologic activity, possess a much smaller molecular weight than the parent product, and provide the hope that eventual synthesis of a potent ACTH peptide may be accomplished.[4, 5, 31, 58, 64, 107, 175, 176, 185, 188, 189, 193, 194, 226, 236]

Compound F (Kendall): Until recently, compound F of Kendall (substance M of Reichstein) was obtained only by extraction from adrenal glands. But now the biologic conversion or biosynthesis of compound F from substance S (Reichstein) is being accomplished,[120, 127, 222] as is also the synthetic production of compound F from a precursor of compound E.[226]

Development of a Rational (Physiologic) Method of Administration. As stated above, the development of a rational or physiologic method for the administration of these hormones will not be fully accomplished until more has been learned about the physiology of the pituitary and adrenal glands in the diseases which respond to these hormones, and about the metabolism of cortisone, hydrocortisone (compound F of Kendall) and ACTH in health and in disease.

One of the prime requirements is the development of satisfactory biologic or biochemical methods for estimating the amount of these substances in bodily fluids and tissues. Thus we could learn how much of them is produced by the pituitary and adrenals of normal persons, or of patients with rheumatoid arthritis or other diseases. The present chromatographic methods are useful, but simpler, more refined methods are desired.[238]

* The price was reduced to $30.00 per gram in April, 1951, to $25.00 per gram in October, 1951.

Much more must be learned about the function of the pituitary and adrenal glands in rheumatic and other patients as compared to normal persons. The majority of investigative rheumatologists and endocrinologists are assuming that the pituitary and adrenal glands are functioning normally in most rheumatoid patients, the conclusion being based chiefly on eosinophilic responses to a single injection of exogenous ACTH (Thorn test),[209] and on studies of urinary steroids.[291, 310, 311] But the fact that the adrenals of most rheumatoids apparently secrete normal amounts of their eosinopenic-producing hormone(cortisone?) under stimulation by exogenous ACTH does not necessarily prove indisputably that the pituitary of the rheumatoid is producing normal amounts of endogenous ACTH, or that the adrenals of the rheumatoid are, without such added stimulation, producing normal amounts of cortisone or cortisone-like material. And, of course, what are normal and adequate amounts for a healthy person may not constitute adequate amounts for the ill.

Despite the fact that studies of the histologic structure of glandular tissues do not always permit one to form precise opinions as to their physiologic potency or normalcy, a more comprehensive study of the histology of the pituitary and adrenal glands of rheumatoid patients (also of others who respond to these hormones), and "normal" persons—for example, persons killed in accidents, and so forth—must be made at necropsy. Are the pituitary and adrenal glands of rheumatoids normal histologically, or are there some (primary or secondary) evidences of disease therein? A British investigator [237] has recently recorded his belief that there may be a characteristic histologic abnormality in the pituitary of rheumatoid arthritics, an abnormality not found in controls. Others have recently reported the presence, in rheumatoid patients, of certain abnormalities in the metabolism of steroids which may indicate a faulty secretion or an abnormal metabolism of the adrenocortical hormones in this disease.[74, 75, 76, 205, 276] If true, the significance of these abnormalities remains to be determined.

From studies made with cortisone or ACTH labeled with radioactive isotopes, much could be learned about the metabolism of these hormones. ACTH tagged with radioiodine and injected into the heart of animals passes at once into the adrenal cortex, where the radioactivity remains for about two hours in rapidly decreasing amounts.[277] Studies with cortisone labeled with tritium, a radioisotope of hydrogen, are also being made.[51] By these and other methods, it may someday be possible to determine whether there is, at the tissue level, a decreased utilization or an increased requirement for cortisone.

Characteristics of Substance X. Until some of the abovementioned investigative methods have been developed we cannot test adequately the hypothesis that the effective substance X of jaundice and that of pregnancy are identical, and that either or both are cortisone (or compound F). Cortisone or compound F is presently the most likely candidate for sub-

stance X. The characteristics of substance X are (1) that it is antirheumatic and antiallergic, that, in other words, it is group specific rather than disease specific; (2) that it develops rapidly in jaundiced patients, more slowly in pregnant patients, and appears to operate in these patients during a characteristic period of time, and (3) that its clinical effects are accomplished rapidly and are more or less complete, but are transient. Cortisone appears to possess most of these characteristics. But in the light of our newer knowledge we must study the pituitary-adrenal relationships during the changing phases of (natural and experimental) jaundice and of pregnancy in rheumatic and nonrheumatic patients. Similar studies should also be made in rheumatoid patients receiving gold salts. Thus we may learn how pregnancy and jaundice (and, much less commonly, gold salts) provide their benefits. We must test rigidly the validity of the interesting but unproved assumptions that in pregnancy the production of cortisone may be markedly increased,[2, 70, 137, 208, 312, 319] and that in hepatitis with jaundice the normal (?) process of inactivation or destruction of cortisone, perhaps by the liver, may be lessened, with a resultant relative increase in cortisone.[70, 87, 137, 288, 329] (No evidence of increased adrenal activity, as revealed by studies of urinary steroids, was found by Sprague, Mason and Power [290] among seven men and nine women with jaundice due to obstruction, cirrhosis or viral hepatitis.)

Empiric Use of Cortisone and ACTH

Clinical investigators, while waiting for the collection of these missing data and for the development of these needed methods, can do much to insure the reasonably intelligent and safe, even though empiric, use of these hormones. Long-term studies of various plans of administration may show how to provide the greatest relief with the least risk, and may even show how to project the hormonal effects farther into the posthormonal period than seems possible now. Clinical and metabolic studies of the effect of repeated small doses of cortisone or hydrocortisone given orally may also constitute another step in the direction of developing the most physiologic method of administration.

During the past year I have often been asked, "Do you think we shall be able to use these or similarly effective substances with safety, or to reproduce continuously the benefits of pregnancy or jaundice?" I believe that we shall. The pregnant woman develops a strikingly altered and improved physiologic state which is generally antagonistic to the continuation of the symptoms of rheumatoid arthritis. She normally tolerates this altered, antirheumatic state for months without any disturbing evidences of hormonal imbalance (unless her white striae are somewhat analogous to the red striae of hypercortisonism). Indeed, she often feels "better than I have for years." As we learn of the agent and mechanism responsible for her antirheumatic state, so we may learn to reproduce that basic mechanism for the physiologic good of others.

Conclusion

Cortisone and ACTH today represent unframed pictures. No boundaries can yet be established to define either their full potentialities or their limitations. These hormones still belong to the physiologist and to the clinical investigator as much as, if not more than, to the practicing physician. But as Professor Starling said many years ago, "The physiology of today is the medicine of tomorrow." [294]

But whatever the immediate or future destiny of these hormones may be in the field of practical therapeutics, they already have demonstrated clearly the potential reversibility of many disease processes thought heretofore to be more or less relentlessly progressive. Thus they have given a sound basis for much hope. In particular, they constitute powerful tools with which we can investigate many problems related to the etiology and treatment of a wide variety of diseases.

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THE RÔLE OF ELASTIC TISSUE IN THE FORMATION OF THE ARTERIOSCLEROTIC LESION *

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ARTERIOSCLEROSIS is currently believed to be a metabolic disorder, a disturbance of cholesterol metabolism which, by some obscure means, leads to accumulation of cholesterol in the lining of arteries. It is further proposed that aging is not a factor in the genesis of arteriosclerosis, since fatty plaques can be experimentally produced in some animals at any age.

This concept of arteriosclerosis is not entirely satisfying. It does not explain the fact that some plaques are entirely fibrous and do not contain cholesterol; it does not explain the focal nature of arteriosclerotic lesions, the greater severity of lesions in the abdominal than in the thoracic aorta, the relative resistance of some arteries, such as the pulmonary, to plaque formation. Nor does it explain the connection between cholesterol metabolism and luetic aortitis, or mitral stenosis, both of which characteristically are associated with severe arteriosclerosis.

More fundamental than such pointed questions is one simple, hard fact: Young people seldom die of coronary or cerebral thrombosis. On the other hand, after the age of 45 most of us can expect to succumb to cardiovascular disease.

This point can be graphically documented by examination of Dublin's data on the death rate in the United States for cardiovascular-renal diseases only (figure 1). This category of diseases includes intracranial lesions of vascular origin, diseases of the heart, arteriosclerosis, high blood pressure and nephritis. The death rate is basal during the first three decades of life, begins to climb in the fourth decade and soars rapidly thereafter. Unfortunately, our colleagues who study the cholesterol metabolism of rabbits and chickens tend too often to forget this obvious link between aging and cardiovascular disease.

The question we must deal with is not whether age is a factor in the genesis of arteriosclerosis—this is a fact—but rather *what* factor in aging, direct or indirect, instigates plaque formation. This discussion will present data which will indicate that (1) there are characteristic age changes in the arterial wall, and (2) that these age changes in the arterial wall apparently precede cholesterol accumulation in the intima.

For the purposes of this discussion, aging will be defined as any change with time in the adult organism. To attempt a more specific definition is to court difficulties, largely because adequate data are not available to permit

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greater exactness. We really cannot distinguish degenerative changes from true age changes. By general connotation, true age changes are those inherent in the organism and presumably inevitable. The point is that, for the time being, and until many more data on aging develop, we can only describe changes that correlate with the passage of time, without stipulating that one is degenerative disease, another endogenous aging. It may well be that the changes ascribed here to aging may be a product of exogenous insults accumulating with time. It may also be that the changes with age in arterial elastic tissue may constitute inevitable endogenous aging. I doubt that the latter is true.

One does not have to look further than the elastic tissue of arteries to find consistent and significant age changes which correlate with the incidence of atheromatosis. In this report, particular emphasis will be placed upon the elastic tissue changes with age in elastic arteries, because they

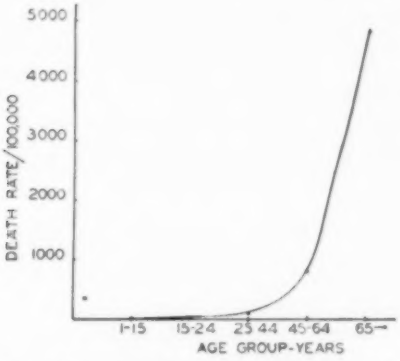

FIG. 1. Death rate from cardiovascular disease in the United States, in various age groups. (Plotted from Dublin's data, Length of life, 1949, Ronald Press, New York.)

lend themselves to quantitation. It should be kept in mind that muscular arteries show elastic tissue changes comparable to those found in elastic arteries like the aorta and differing only in detail from the latter. For example, in the human coronary artery one finds, at the age of, roughly, 20 years, progressive splitting and fraying of elastic fibers of the internal elastica. The frayed and fragmented elements of the elastica interna gradually work their way into the muscular media, and as age progresses they accumulate in this new site. In addition to a shift with age in location of elastic tissue, there appear also to be chemical changes. The frayed elastica interna and the elastic tissue located in the media stain more densely and have a very profound affinity for calcium. The latter is readily demonstrated by dark-field examination of microincinerated sections.

While such elastic tissue changes can exist in the coronary artery in the absence of underlying plaque formation, we have not as yet seen the existence of plaques without the underlying elastic tissue calcification. Comparable progressive deterioration and calcification of medial elastic tissue have been described in other major vessels, such as the renal and hepatic arteries (figure 2). These differ from one another only in whether the inner or outer elastica is involved, or both, and also in the rate of elastic tissue change. But in all of the vessels studied, intimal plaque formation almost invariably is accompanied by underlying elastic tissue degeneration and calcification.

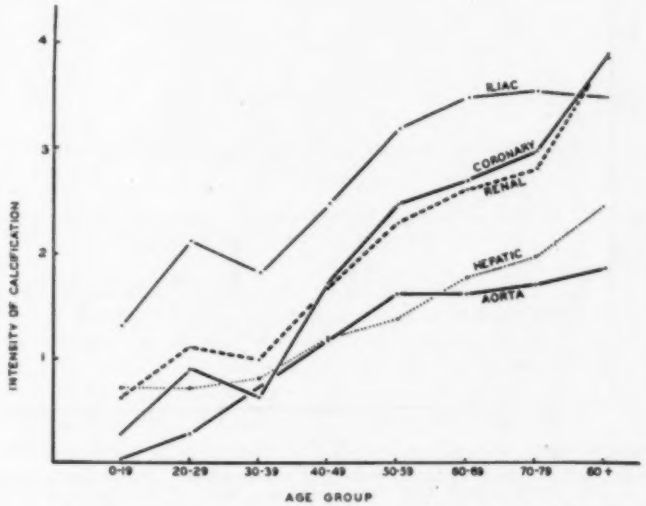

FIG. 2. Age comparison of rates of calcification of medial elastic tissue in human arteries. (From Blumenthal, Lansing and Gray, Am. J. Path. **26**: 989, 1950.)

Returning to examination of the aging of elastic tissue in the aorta, we can note immediately that in elastic tissue in young individuals, individuals less than 20 years of age, there is a characteristic absence of calcium. The elastic plates are thick and flat, and show a minimum of fraying. On the other hand, after the age of 20, and with each decade thereafter, there is an increasing severity of medial elastic tissue fraying and fragmentation. This altered elastic tissue is often granular and, as seen by dark-field examination of microincinerated preparations, profoundly calcified.

A comparison of the age changes in several different vessels, muscular and elastic, shows very clearly that all conform to a common pattern. The intensity of calcification of all these vessels increases steadily with age. Most

striking is the fact that the age deterioration of elastic tissue does not begin in advanced senility or even in late middle life. This age change in arteries begins early, at about the age of 20, and climbs steadily thereafter.

Quantitative data can be obtained by the extraction of elastin from aortas which have had the adventitia and intima removed. The media so obtained is heated at 98° C. in 0.1 normal sodium hydroxide for 45 minutes. Elastin remains as an insoluble fraction after this treatment, while other organic constituents of the media are destroyed. Such elastin retains its specific tinctorial reaction with elastic tissue stains, and the calcium in association with the elastic fibers remains in this elastin.

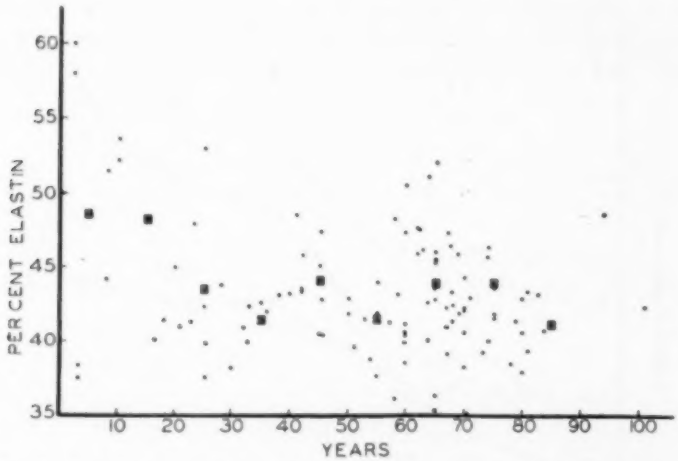

FIG. 3. Age variations in elastin content of human aortas. Except for the first two decades of life, which suggest high elastin contents, there is little variation in elastin contents with age.

The results obtained by this procedure on aortas varying in age from still-born to over 100 years are summarized in figures 3 and 4. Our data indicate that, at least after the age of 20, there is no significant loss of elastic tissue with age, the elastin content of the media of individual aortas varying between 41 and 44 per cent. During the first two decades of life the elastin values are somewhat higher, but this may be due to the relatively small number of analyses performed. The calcium analyses yield very impressive data. From birth up to 20 years, calcium content of the arterial elastin is but a fraction of 1 per cent. In the third decade of life, the calcium level rises to 1.2 per cent and continues to increase steadily thereafter to values in the neighborhood of 6 per cent of the dry weight of elastin. The loss of arterial elasticity with age may well be a function of the calcification of elastic tissue rather than a result of loss of elastic tissue.

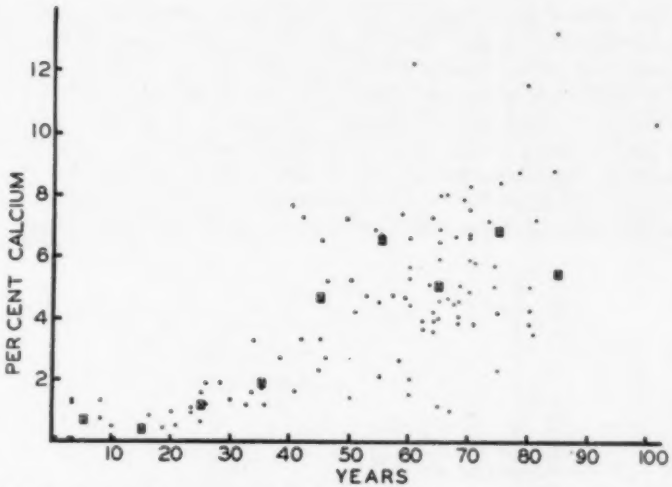

FIG. 4. Variations with age in calcium content of elastin in the media of human aortas. Analyses were performed on dried, defatted elastin.

In these analyses, no attention was paid to the condition of the intima (presence or absence of plaques), and as a consequence it might be pointed out that perhaps the changes in elastic tissue are a result of changes occurring in the intima. To preclude this possibility, the calcium content of medial elastin was determined from plaque-free areas of human aortas of a wide age distribution in an entirely independent series of analyses (figure 5). In the absence of apparent intimal change, the data have illustrated a progressive rise in the calcium content for elastin, which again was sig-

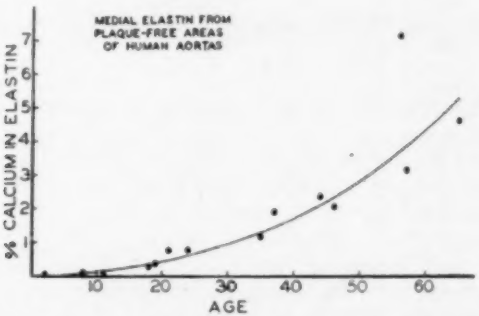

FIG. 5. Age variations in calcium content of elastin in the media of human aortas grossly free of atheromata. Data calculated on a dried, defatted basis.

nificantly altered at the age of 20. Calcification of arterial elastic tissue is a true senescent change. It occurs as noted in the absence of intimal involvement, but the converse is not equally true.

The pulmonary artery lends itself very well to evaluation of the rôle of elastic tissue in human arteriosclerosis. Although it is an elastic artery like the aorta, and has its origin close to the heart, it differs very markedly from the aorta in that atheromata are not usually found in the pulmonary artery at any age. If, as we believe, the calcification of medial and elastic tissue is essential to intimal plaque formation, then the senile pulmonary artery lack-

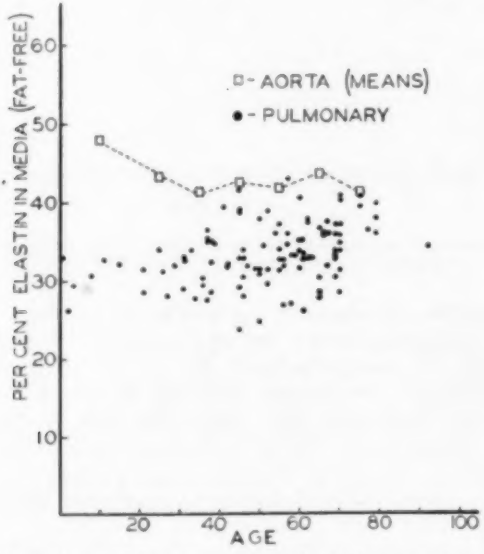

FIG. 6. Elastin content and its age variations in the human pulmonary artery compared with similar data from the aorta. (From Lansing, Rosenthal and Alex, J. Gerontol. 5: 211, 1950.)

ing atheromata should also be relatively free of elastic tissue calcification. Elastin was again prepared from pulmonary arteries, following the procedure already referred to, and, as might be expected, the elastin content of this vessel remained constant with age, with a mean level of 33 to 35 per cent (figure 6), somewhat less than is found in the aorta.

A comparison of the calcium content of the pulmonary artery with that of the aorta is very impressive (figure 7). The calcium increase with age is almost imperceptible. The age group 70–79 years showed a mean concentration of calcium in elastin of 0.66 per cent. This amount of calcium is comparable to that found in the aortas of adolescents. We have been

fortunate in acquiring a number of pulmonary arteries from individuals with histories of mitral stenosis. In such pulmonary hypertensives there are gross, fatty, intimal plaques in the pulmonary arteries. Again, if our reasoning is sound—that medial elastic tissue calcification instigates plaque formation—we should find significant levels of elastic tissue calcification in the pulmonary arteries of individuals with histories of mitral stenosis and with accompanying atherosclerosis of the pulmonary artery. In the accompanying figure it will be noted that two calcium analyses are conspicuous in that they represent values of 2 and 3 per cent. Both of these represent cases of mitral stenosis.

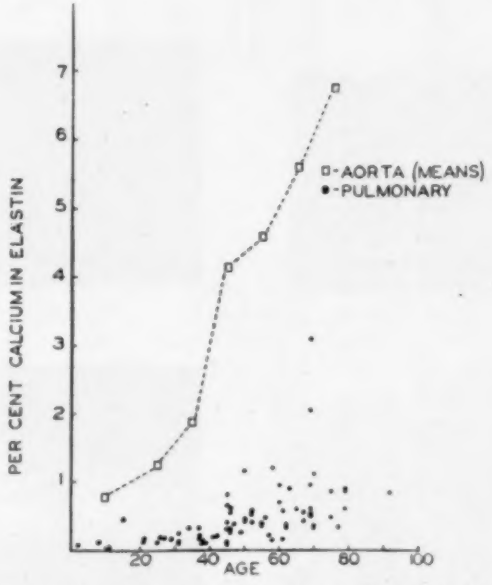

FIG. 7. Increase of calcium content of pulmonary arterial elastin with age compared with values for the aorta. Note the marked difference in calcification with age in these vessels. (From Lansing, Rosenthal and Alex, J. Gerontol. 5: 211, 1950.)

The analytic data closely parallel those obtained in microscopic sections (figure 8). Elastic tissue stains of normal young and old pulmonary arteries indicate little or no age change in the morphology of the elastic lamellae. Similarly, there is essentially no increase with age in calcium content of the elastic lamellae. However, in cases of pulmonary hypertension there is marked calcification of the elastic lamellae in addition to plaque formation. Figure 8 includes a section of the pulmonary artery of a 69 year old male with a history of mitral stenosis which illustrates this point.

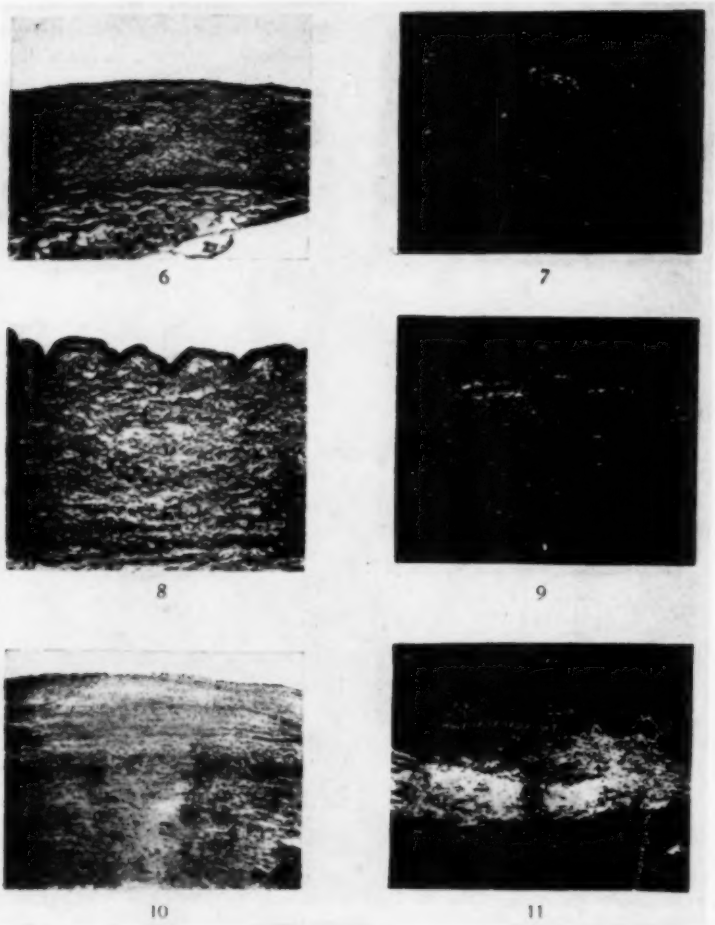

FIG. 8. Elastic tissue and calcific changes with age in the human pulmonary artery. Numbers 6, 8 and 10 were stained with resorcin-fuchsin and are from ages 21, 67 and 69, respectively. Numbers 7, 9 and 11 were microincinerated and photographed in dark-field, and represent adjacent sections from the 21, 67 and 69 year old specimens, respectively. In the absence of atheromata (8 and 9), there is also an absence of calcification.

These data indicate that the pulmonary artery, which is normally resistant to plaque formation, also is resistant to elastic tissue calcification. When plaques do form in the pulmonary artery, they are accompanied by underlying elastic tissue calcification.

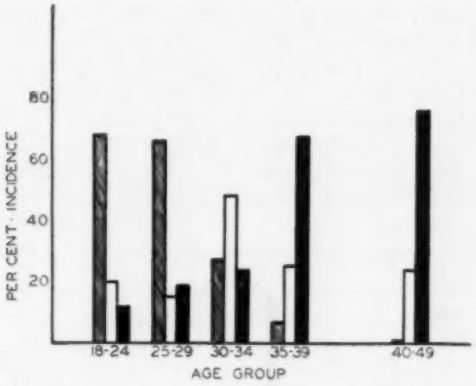

FIG. 9. Age incidence of fibrous, fatty and necrotic plaques in human coronary arteries. Fibrous = diagonal markings, fatty = white bars, and necrotic = black bars. (Plotted from data by Yater et al., Am. Heart J. **36**: 334, 481 and 683, 1948.)

There is another type of descriptive evidence which supports our general thesis. In the human, because it is obviously impossible to trace the genesis of a single plaque, it is necessary to employ the method of seriation, i.e., the establishment of a series of plaques graded by severity to infer the probable sequence of events. The cholesterol content of a plaque is a reasonable index of its age and severity. There is, as we all know, considerable controversy as to the relation between fibrous, fatty and necrotic plaques. Karsner grades severity of intimal plaques from the fibrous as the least severe, through the fatty and necrotic as the most severe. The data of Yater support this view (figure 9). The incidence of fibrous plaques is maximal in young people and progressively decreases with age. As the incidence of fibrous plaques decreases, there is a corresponding increase in the frequency of occurrence of fatty plaques. It is reasonable to believe that the fibrous plaque is usually the precursor to the fatty plaque.

TABLE I

Analyses of Isolated Plaques (Intima), Graded by Severity and Age Group at Autopsy, Showing That Lesions of Similar Gross Appearance May Differ Chemically, Depending on Age of the Individual

Severity of Lesion	Per Cent Calcium*		Per Cent Cholesterol*	
	Age 30–59	Age 60–80	Age 30–59	Age 60–80
Normal	0.17	1.54	1.9	3.2
Fibrous	0.61	1.62	8.5	24.8
Fatty	6.62	6.17	29.9	29.3
Necrotic	5.56	10.90	47.8	24.5

* On fat-free dry weight basis.

A similar conclusion may be reached from the data obtained by a chemical analysis of isolated intimal plaques. We carefully excised and collected from aortas a series of plaques from a group of young and also from a group of old individuals. The intima was separated from media and adventitia. The essential point, as can be seen in table 1, is that the chemical composition of grossly similar plaques changes with age. Thus, the fibrous plaque in the old age group contains three times as much cholesterol as in the young group. The fatty plaques in both age groups are similar in both cholesterol and calcium contents. The necrotic plaques, however, show a sharp increase of calcium and arithmetically, therefore, a decrease in choles-

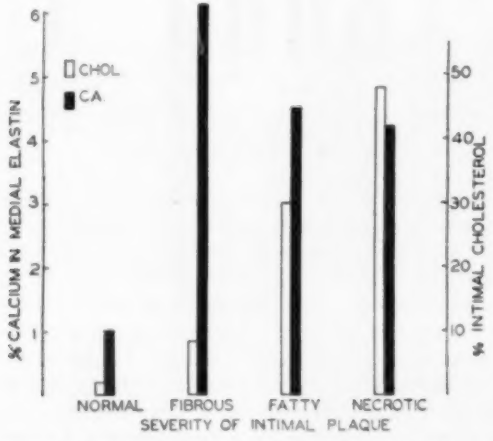

FIG. 10. Histogram of calcium and cholesterol analyses in a series of plaques graded by severity. Calcium is expressed as percentage in dry, defatted medial elastin, cholesterol as percentage in dry intima. On the basis of this seriation, calcium in the media appears to increase before cholesterol. (From Lansing, Alex and Rosenthal, J. Gerontol. **5**: 314, 1950.)

terol. These data again support the belief that the first intimal lesion is the fibrous plaque, which progressively accumulates cholesterol to become the fatty plaque, which in turn ulcerates and calcifies.

On the basis of such seriation, and appreciating the limitations of this procedure, we have collected a graded series of plaques from a single group (30–59 years). After isolating the lesion, we separated intima from media, having previously removed the adventitia, and analyzed the cholesterol content of the intimal lesion and the calcium content of the underlying medial elastin. The data are graphically represented in figure 10. Cholesterol shows a progressive rise, which reaches substantial proportions in the fatty plaques and climbs even higher in the necrotic lesions. On the other hand, the degree of elastic tissue calcification reaches a maximum in the transition

from normal to fibrous intima and declines thereafter. These data strongly suggest that we are dealing with two temporally and quantitatively distinct reactions. The medial elastic tissue calcification probably precedes the plaque formation, since the calcium accumulation is associated with the transition from the normal to a fibrous lesion, whereas the cholesterol deposition becomes striking only in the later stages of plaque development.

In summary, arteriosclerosis appears to be a dual process, involving aging of the arterial wall and cholesterol accumulation in the intima. Calcification of senescent elastic tissue in the media occurs with or without atheromatosis. When the two co-exist, analyses indicate that cholesterol accumulates in the intimal plaque after the underlying media has undergone elastic tissue calcification. What factors condition the age change in chemical composition of elastic tissue remains to be determined. Nothing in these data should be interpreted to mean that altered cholesterol metabolism is not a factor in arteriosclerosis. We wish only to stress that aging of the arterial wall establishes a substrate for penetration and accumulation of cholesterol. It is possible that, without such changes in the arterial wall, cholesterol will not accumulate in the lining of arteries.

ACKNOWLEDGMENT

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PHOSPHATE ESTER POISONING, A NEW PROBLEM FOR THE INTERNIST*

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Within the past three years, several esters of phosphoric acid have been manufactured and applied on an expanding scale because of their exceptional effectiveness as agricultural insecticides. Requirements for this purpose have increased rapidly, in spite of a high toxicity for man and other animals, because these compounds have already played a vital rôle in the economically important task of protecting food and other crops from the ravages of insects. Such damages amount to billions of dollars annually. Some of the phosphate esters are peculiarly effective for this purpose, to an extent equaled by none of the former crop protection chemicals, because of a sharply defined specificity in mode of action. They quickly attack agricultural insect pests, as well as all other forms of animal life, in amounts that are not at all harmful to plants or dangerous to man as food residues. The same properties that make these phosphate esters effective for the destruction of insect pests also make them dangerous for human life, unless intelligent care is exercised in their handling and use. Ignorance of their properties, or carelessness, invites accidents. The large scale manufacture and application of these biologically active chemicals under diversified conditions have already resulted in a number of acute transient parathion poisonings, and even fatalities, during the early stages of development. As knowledge of the biologic properties and necessary protective measures has been expanded, the safety record has improved, although with the first large scale use, in the growing season 1949, there were in this country a number of acute parathion poisonings, as well as three fatalities in processing plants and three in the field. The initial South American record among unskilled users of a parathion insecticide from Europe was even less fortunate. In the year 1950, with still wider use and much higher tonnages in agricultural applications, the number of reported and substantiated transient toxic reactions had greatly diminished and no fatalities at all are known to have occurred in the United States. The 1950 record in this country thus compares rather favorably with earlier experience with nicotine, hydrogen cyanide and several less toxic compounds.

Although rigid adherence to necessary safety practice has made possible a large scale application of the existing anticholinesterase insecticides, the search for dusting and spray chemicals without important toxicity for warm blooded animals has of course continued. Early progress in this direction

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was made in the discovery of the pyrethrins in prior years and in the patent of Muller disclosing the insecticidal properties of DDT. Both these developments have been major advances in the desired direction, although limited in value in each case by a too selective action against many of the pests for which control measures were required. The possibility that screening of phosphate esters by simple in vitro tests might reveal a compound more effective against the cholinesterase of insects than that of man has been suggested by Metcalf and March's demonstration [1] of a compound, *diisopropyl p-nitrophenyl thiophosphate*, whose potency against cholinesterase from the fly brain was far greater than against the corresponding enzyme in bee or mouse brain tissue. Some attempts have been made to produce less toxic cholinesterase-inhibiting insecticides without demonstrating any species difference in enzyme potency. Such insecticides, although less toxic for man, may also be less toxic for insects. The practical development of these newer experimental phosphate esters therefore awaits critical evaluation from this angle.

The early history of the discovery of the cholinesterase-inhibiting action of certain phosphate esters—in Dale's laboratory at Cambridge, dating from 1941—is now well known. Subsequent investigation of several of these compounds, among which *diisopropyl fluorophosphate* (DFP) was among the more potent, continued under the military secrecy of World War II in both the Axis and the Allied camps, where their possible application as war gases was being considered. Several compounds of the group were developed in Germany during World War II by Schrader and tried in the field as insecticides in the belief that their "nicotine-like" properties would be effective. Postwar trials in several countries resulted in a very favorable experience with respect to insect control but some unfortunate consequences among investigators and users unfamiliar with their biologic properties. The first of these compounds to receive extensive agricultural trial was *hexaethyltetraphosphate* (HETP), a compound now believed to break down rapidly into a highly effective but unstable cholinesterase inhibitor of fairly high volatility, *tetraethylpyrophosphate* (TEPP). TEPP in turn was tried in insecticide formulations and found to be potent but somewhat unstable in agricultural use. A nonvolatile and relatively stable cholinesterase inhibitor, *o,o,p-nitrophenylthiophosphate* (parathion), has been consistently effective, although dangerous unless used according to strict safety rules. Parathion in the pure or technical grade is an oily liquid presenting little vapor hazard, the maximal vapor concentration at 80° F. being only 0.6 micrograms per liter of air, but an important skin absorption hazard. The vapor pressure is 0.000028 mm. of mercury at 24° C. Actual amounts of parathion required for effective insect control are small and therefore, in field use, technical grade parathion is diluted with a solvent, or is adsorbed as a 15 per cent to 25 per cent concentrate on a wettable powder. For field use, one to three pounds of a 15 per cent or 25 per cent parathion wettable

powder, or one pint of a 25 per cent emulsifiable liquid formulation of parathion, is added to 100 gallons of water as a spray. Other phosphate ester insecticides have been applied mainly as emulsions, and in comparable concentrations. There has been no problem with respect to residue toxicity where sprays or dusts have been applied according to schedules approved by the U. S. Department of Agriculture.

Among the potent cholinesterase inhibitors of potential interest to the internist, it may be desirable to mention the so-called nerve gases, which have been publicized as possible war weapons but which are still under some degree of military secrecy with respect to identity and properties. The practical experience with cholinesterase-inhibiting insecticides, in plants and in field use, is of value as a guide to planned medical preparation for attacks involving the use of such nerve gases as may be similar in biologic action to some of the new insecticides. Recommended emergency therapy and protective measures, as outlined in the Health Services and Special Weapons Defense Manual released by the U. S. Government Printing Office on December 27, 1950, are parallel, in many respects, to measures already in use in connection with potential hazards in the manufacture or agricultural application of phosphate ester insecticides.

Variations in potency and biologic effectiveness of the several well studied phosphate cholinesterase inhibitors have been mainly quantitative, and to a slight degree qualitative, according to the structure, stability, solubility and volatility of the molecule. The pharmacology of the group as a whole is now relatively well defined from studies patterned from work on DFP and similar agents which have served as investigational tools for the experimental neurophysiologist since this subject was declassified at the end of World War II. To summarize their action briefly, these phosphate esters have resembled physostigmine in their ability to inactivate cholinesterase by combining with this enzyme, in stoichiometric proportions, to form a compound which has neither enzyme activity nor any known toxicity. They differ in having a less graded effect according to dose. Several active cholinesterase inhibitors, notably DFP, TEPP and parathion, have also been far more potent than physostigmine, and have been more lasting in their effects. Each has been found to combine irreversibly with cholinesterase. The block of this enzyme by physostigmine, on the other hand, is only temporary, and readily reversible by dilution or dialysis. The muscarine-like, curare-like and nicotine-like actions of the phosphate esters on animals are in actuality, therefore, symptoms of an intoxication by endogenous acetylcholine, which normally forms at the nerve synapses, but which the chemically inactivated cholinesterase enzymes of the nervous system can no longer destroy. Animals killed by these agents have virtually no cholinesterase activity but high concentrations of acetylcholine in the tissues of the nervous system.[1] No other clearly significant postmortem findings have been described in experimental animals or in human autopsy material, with

the exception, in a few instances, of the demonstration of secretions in the bronchi which apparently resulted from overactivity of the parasympathetic innervation. Where the history is ambiguous, a differential diagnosis, as from a coronary occlusion or other acute illness, may often be difficult without cholinesterase tests.

Possible modes of action other than that on the enzyme have been postulated only on the basis of rather unsubstantial evidence. The finding of cerebral edema and a pressure cone of the medulla, in an autopsy case, has been cited by Grob et al.[3] as not yet fully explained. They have also mentioned other minor features, such as a slight leukocytosis. However, experimental animals have not shown such effects, and to date no clearcut indications of any action other than that on the cholinesterase enzyme system have been available from published reports of animal experiments or human experience. Quantitative clinical data on the pharmacology of DFP and TEPP have been collected by Grob and others in the therapy of myasthenia gravis, paralytic ileus and glaucoma. Comparable data on parathion and some of the other cholinesterase inhibitors still await such detailed investigation.

The signs and symptoms of phosphate ester poisoning, as observed in man, have never been found except in association with a profound depression of plasma and red cell cholinesterase activity. They have included giddiness, headache, confusion, weakness, nausea, vomiting, cramps, diarrhea, sweating, pupillary constriction, occasionally an irregular pulse, and often a sense of constriction in the chest. Other miscellaneous disorders of nervous function have been frequent. No topical actions on skin except local warmth and sweating have occurred, but absorption through skin is rapid. In field use, topical effects on the eye have been less common with parathion than with more volatile phosphate esters. Profound intoxication has been characterized by generalized muscular twitches, prostration, coma and a progressive pulmonary congestion resulting from bronchial muscular constriction or excessive secretion in the bronchi. The clonic type convulsions reported in a few instances are not dissimilar to those frequently described as a complication of acute anoxia from other causes. Symptoms develop only during, or within a few hours of, exposure and subside completely within a day or two.

Many incidental illnesses among handlers of phosphate esters raise a problem in differential diagnosis. However, a positive confirmation of the diagnosis of poisoning by a phosphate ester can be made on the basis of tests on the plasma, red cells or other tissues for cholinesterase activity. Single or repeated exposures to amounts too small to produce symptoms can deplete plasma and red cell enzyme activities to values far below a preëxposure control test or normal average values, but symptoms occur only in association with a profound drop in these values, usually to 30 per cent of normal or lower. Following absorption by any route, plasma values fall and re-

cover quickly, red cell values more slowly. It has been postulated that the red cell activity in animals recovers at a rate somewhat comparable to that of the tissues. Susceptibility, as distinguished from allergic sensitivity, to small doses persists to a diminishing degree as the enzymes regenerate and the plasma and red cell values approach normal. This process is rapid in the first few days, but may require weeks for completion in the case of the plasma and still longer, at average rates of 1 or 2 per cent a day, in the case of the red cells. There is, therefore, a danger from repeated small exposures and from new exposures during convalescence from a previous poisoning.

An effective program for prevention of accidental poisoning by phosphate ester insecticides requires meticulous attention to protective measures against skin contact or inhalation of airborne sprays, and a regular testing schedule for plasma and red cell samples if there is even a remote risk of exposure, as in manufacturing or spray operations. Such testing is extremely simple, all that is needed being a finger-tip sample of capillary blood collected in a heparin-coated melting-point tube of 1 mm. diameter. The plasma and cells are separated by centrifuging this capillary, and are analyzed separately by the short and reliable electrometric procedure of Michel.[4] This procedure actually involves nothing more than an accurate mixing of the reagents and a glass electrode pH determination before and after a period of incubation at a control temperature. Routine testing at weekly or shorter intervals can detect danger before injury or symptoms appear, as has been done successfully in California citrus groves, where very heavy insecticidal dosages of parathion were being applied for many weeks in succession. Depression of individual activities by 10 per cent or more below preëxposure controls or normal averages may be significant. Because of the variations in normal values, in either a plus or minus direction, particularly in the plasma, a preexposure normal as a base line may be of great value. Averages of exposed groups of sufficient size may also be quite useful.

If acute poisoning does occur, the problem of effective therapy is urgent and immediate. The poisoning is strictly an acute episode. No time can be squandered in the search for special drugs, or transportation to a hospital, without grave risk to the patient. Depending on the magnitude of the exposure, the outcome may be determined in a matter of hours or even minutes. If recovery does occur, it is followed by no sequelae other than a gradually diminishing susceptibility to the action of any phosphate ester during the interval of enzyme regeneration. Symptoms disappear completely while the enzyme activity is still at but a small fraction of normal. Neither blood nor concentrated esterase has proved effective for treatment. Assuming a molecular weight of 400,000 for cholinesterase and 323 for parathion, it would require 1,250 mg. of cholinesterase to neutralize each milligram of parathion present.

The specific antidote of proved effectiveness for both the experimental animal and man is atropine, given at once, by any convenient route and in

large amounts. Other atropine-like drugs are of theoretic value but have not been tested. If severe poisoning occurs, the initial dose should be 1 or 2 mg., and this should be repeated in successive additional doses of comparable magnitude until enough has been given to cause a dry mouth and to block the action of the parasympathetic innervation of the bronchi. General supportive measures, such as postural drainage or oxygen therapy, are also indicated if the patient is cyanotic. Atropine counteracts only the parasympathetic component of the generalized overactivity of the nervous system caused by cholinesterase inhibitors, but this action may be lifesaving. The 2 mg. ampules of atropine recently distributed for civil defense purposes are well suited for the emergency treatment of an acute phosphate ester insecticide poisoning. Some readily accessible supply of atropine, with proper directions for emergency use, is just as important for the safety of persons handling phosphate esters as a fire extinguisher is on a boat, but specific precautions should be taken to discourage prophylactic use or other misuse of such supplies as made available by the physician or other individual responsible for the safety of persons handling these compounds. It is obvious enough that any man taking atropine prior to risking exposure may thereby deprive himself of the warning symptoms which might otherwise permit the timely application of therapeutic measures.

On no occasion is there any excuse for or advantage in minimizing the hazards which may result from careless use of these biologically active crop protection chemicals. In skilled hands, and in the light of a good understanding of their biologic properties, the phosphate ester insecticides have done an important job and should continue to do so safely until the day arrives when a truly less toxic but equally effective insecticide can be found.

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BACTEROIDES INFECTIONS *

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There is probably no subject in modern medicine more neglected than that of Bacteroides-caused infections. Recent textbooks of internal medicine, surgery, obstetrics, urology, otolaryngology, and even bacteriology scarcely mention this condition. Yet 35 such cases have been observed at the John Gaston Hospital in the past five years. It is our impression that Bacteroides infections occur much more frequently than would be concluded from a review of the literature. There are many reasons why infections with these organisms may go undiagnosed. The textbooks of bacteriology give little or no information concerning them, so that it is quite difficult for the average laboratory worker to identify these organisms even when they are isolated. Since Bacteroides are anaerobes, they are overlooked unless the material is studied by anaerobic methods, and, therefore, very frequently a negative report is obtained. Probably the chief reason why these infections are not diagnosed, however, is that they are not considered. It appears that many physicians are entirely unacquainted with the significance of Bacteroides.

Since these bacteria may be the predominant organism in adult feces,[1] there is an illogical tendency to regard their presence in the blood or in suppurative lesions as of no clinical significance. Time and again one hears that Bacteroides are merely nonpathogenic contaminants. Yet the pathogenicity of these organisms was well demonstrated in experimental animals, in 1934, by Thompson and Beaver;[2] and, until recently, *Bact. funduliformis* septicemias in man were usually fatal. It is our opinion that many serious septicemias of unknown etiology are caused by these bacteria; this would seem to be especially probable following surgical procedures involving the intestinal and genitourinary tracts.

Castellani and Chalmers,[3] in 1919, proposed the designation of Bacteroides for a large group of anaerobic, nonsporulating bacilli. Today, there is no more confused chapter in the field of bacteriology than that dealing with these organisms. The 1948 edition of "Bergey's Manual of Determinative Bacteriology"[4] states that its section on Bacteroides has been completely revised, so that it recognizes 23 definite and three possible species. It classifies Bacteroides as motile or nonmotile, strictly anaerobic, gram-negative, nonsporulating rods which may or may not require enriched culture media. In an attempt to clarify this situation, a paper is being prepared

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at this institution which embodies a more fundamental classification of these organisms.[8]

Bacteroides are normal inhabitants of the mucous membranes of the body, and injury of mucosal surfaces may result in localized or widespread infection. These organisms were first reported in 1897 to be the etiologic agents in various suppurative lesions by Veillon and Zuber [6] and by Halle.[7] The first two investigators obtained Bacteroides from acute inflammatory processes involving the appendix and other organs, while Halle simultaneously identified these bacteria in suppurative processes involving the female genital tract. In 1931 and 1932, Thompson and Beaver [2] reported two fatal cases of bacteremia due to Bacteroides. In reviewing the literature at that time, they found that 10 cases of bacteremia due to these organisms had been reported. Cohen,[8] in 1932, studied 16 cases of abscess of the lung bacteriologically and found that *Bact. melanicogenicum* was present in 14 cases, while *Bact. fragilis* was obtained in five instances. Dixon and Deuterman [9] reported the occurrence of *Bact. funduliformis* infection in six patients after operation for carcinoma of the colon. Only one of these recovered. The seriousness of Bacteroides septicemia was further stressed by Brown and his associates [10] when they reported the first recovery in a series of 15 cases. In 1945, Smith and Ropes [11] published an analysis of 20 cases of Bacteroides infections. They pointed out that treatment consisted chiefly of surgical and supportive measures. Ruys,[12] in 1947, reported four cases of Bacteroides septicemia, of which only one survived. In 1949, Beigelman and Rantz [13] reviewed 47 cases of Bacteroides infections and stated that these organisms possessed a considerable degree of resistance to penicillin and streptomycin. Recently, we reported two instances of *Bact. funduliformis* septicemia that responded excellently to aureomycin.[14]

This paper represents an attempt to correlate more adequately the pathogenesis, clinical syndrome and therapy of Bacteroides infections. It is hoped that this may stimulate an awareness of the frequency and potential seriousness of Bacteroides-caused infections. Thirty-five cases which have been observed at the John Gaston Hospital in the past five years are reviewed. These have been divided into six categories, based upon the portal of entry of the Bacteroides organisms.

Bacteroides Infections Originating in the Respiratory System

Six cases are included in this group. All of these patients were critically ill and displayed a spiking type of fever. The period of hospitalization ranged from 12 hours (total illness of three and one-half days) to 59 days. All were Negroes. Four were males and two were females. Three patients died and were studied at necropsy. In two instances, *Bact. funduliformis* was isolated from the blood. In only one patient was icterus noted; this was a case of Bacteroides septicemia which was successfully treated with aureomycin, as reported elsewhere.[14] A leukocytosis was present in all but

one patient. This particular individual was the only one who did not appear well developed and well nourished on admission. He died a few hours after hospitalization and is discussed below (case 2). It is of interest that this was the only patient in this group whose clinical appearance corresponded to the actual seriousness of his infection. In only one case did the Bacteroides organisms play a secondary rôle in the clinical picture; in this particular instance, the basic disease entity was a lymphoepithelioma, with Bacteroides being only secondary invaders.

Case Reports

Case 1. A 20 year old Negro female was hospitalized on August 11, 1945, with the complaints of chills, fever, cough and photophobia. Four weeks prior to admission, the patient had noted the onset of a severe sore throat with an associated low grade fever. This illness was not severe enough to require bed-rest, and after one week the throat was better. However, the patient began to have daily chills with profuse sweating, and now it became necessary for her to remain constantly in bed. Severe photophobia and lacrimation developed. There was associated malaise, myalgia and constant dull frontal headache. During the week prior to admission, dyspnea on slight exertion, vertigo and dark urine had been noted. Concurrently, a painless cough productive of mucus had been observed. Intermittent nausea had been present for several days prior to admission, and the patient had vomited on three occasions.

Examination revealed a temperature of 104° F., pulse 120, respirations 22, and blood pressure 90 mm. of Hg systolic and 0 mm. diastolic. The general appearance was that of a well developed young Negro female who did not appear acutely ill. The mucosa of the pharynx and of the anterior tonsillar pillars was hyperemic. There was a tachycardia of 120, and a soft systolic murmur was heard over the apex. Abdominal examination revealed slight tenderness over the suprapubic area.

During six weeks of hospitalization, the patient suffered repeated severe chills. While the temperature remained septic in character and reached 104° to 107° F. each day, the patient had no complaints other than weakness, malaise and occasional mild nausea. She was given whole blood and glucose intravenously at frequent intervals. Sulfathiazole was administered in doses of 2 gm. initially, and then 1 gm. every four hours. Though repeated thick and thin blood smears failed to reveal the presence of malarial parasites, a therapeutic test with quinine sulfate was carried out, with no clinical response. Two weeks after hospitalization, penicillin therapy was begun, using 20,000 units intravenously initially, and then 20,000 units intramuscularly every three hours. At no time did the clinical picture show a striking alteration. There was a progressive downward course, with advancing weakness and lethargy. Eleven days after admission a pure culture of *Bact. funduliformis* was obtained from the blood. The cough, which had been present for one week prior to admission, became more constant, and about three weeks after hospitalization coarse râles were noted in the bases of both lungs, together with bronchovesicular breath sounds. From this period until death three weeks later, the respiratory rate ranged from 40 to 50 per minute. During the last week of life there were frequent small pulmonary hemorrhages, and during the last 12 hours cough was essentially constant. Approximately one hour prior to death, the patient coughed up large quantities of fresh blood and passed into shock from which she could not be revived.

Laboratory Findings: The red blood cell count varied from 3,200,000 to 1,200,000; the hemoglobin from 9 gm. to less than 7.5; the white blood cell count from 8,200 to 34,200, with a persistent shift to the left. Repeated urinalyses were negative.

The non-protein-nitrogen on admission was 22; the icteric index ranged from 4 to 10. Weekly chest roentgenograms were obtained. The earliest of these showed no parenchymal involvement. Three weeks prior to death, a film of the chest revealed evidence of pneumonic consolidation of the lower left and the middle and lower right lobes. Another film five days prior to death disclosed definite improvement in the pulmonary condition, although there was evidence of fluid with pneumothorax over the region of the left lower lobe. The lesion in the right lower base was definitely improved.

Necropsy Findings: The pericardial sac contained 75 c.c. of translucent fluid. There was a generalized pleural thickening with diffuse adhesions. Patchy areas of consolidation were found throughout both lung fields, with five abscesses which contained foul smelling, purulent material. The largest of these abscesses measured 6 cm. in diameter. The spleen had a wrinkled capsule and a very soft pulp.

Microscopic preparations of the lungs showed diffuse infiltration by large mononuclear cells and lymphocytes. These cells were observed in many alveoli, together with red blood cells. Multiple focal areas of necrosis and polymorphonuclear cells were scattered throughout the lungs. A large number of mononuclear cells were present in the splenic pulp.

Bact. funduliformis in pure culture was isolated from the blood, sputum and the lung abscesses at necropsy.

Case 2. A 64 year old Negro male was hospitalized on November 2, 1948, with the complaints of chills, fever, shortness of breath and pain in the epigastrium. Three days prior to admission, this patient was suddenly stricken with a severe chill which was followed by high fever. A few hours prior to this, he had noted the development of a severe frontal headache. Shortly following the chill, the patient observed a sharp pain across the epigastrium, which was described as knifelike in character. Simultaneously, a cough was noted for the first time. The following day this cough became productive of thick, pinkish-colored sputum. Since the onset of the illness, anorexia, malaise and myalgia had been prominent. There had been no gastrointestinal symptoms.

Examination revealed a temperature of 99.6° F., pulse 120, respirations 50, and blood pressure 120 mm. of Hg systolic and 90 mm. diastolic. The general appearance was that of a well developed, poorly nourished Negro male who was quite dyspneic and appeared to be acutely ill. Pallor of the mucous membranes was noted. The pharynx was moderately hyperemic, and cardiac examination revealed a tachycardia of 120 per minute, with frequent premature ventricular contractions. Examination of the chest revealed a panting, gasping type of respiration with frequent coughing. There was dullness to percussion over the right lower chest. Increased tactile fremitus, coarse râles and tubular breathing were heard over both lung bases anteriorly and posteriorly. The abdomen was slightly distended, and palpation disclosed diffuse tenderness over the epigastric area. The liver, kidney and spleen were not palpable.

Immediately upon admission nasal oxygen was begun, and the patient was placed on 50,000 units of penicillin intramuscularly every three hours. Simultaneously, sulfadiazine was begun, with an initial dose of 4 gm. orally, and then 1 gm. every four hours. Plasma and intravenous fluids were also given as supportive therapy. However, the patient died in respiratory failure 12 hours after admission.

Laboratory Findings: The white blood count was 4,500; hemoglobin 9 gm.; non-protein-nitrogen 54 mg. per cent. The blood serologic test for syphilis was negative. A chest roentgenogram on admission revealed extensive consolidation in both lower lobes (figure 1).

Necropsy Findings: The only significant morbid anatomic changes were in the lungs. Aside from a very narrow margin along the inferior border, the right lower

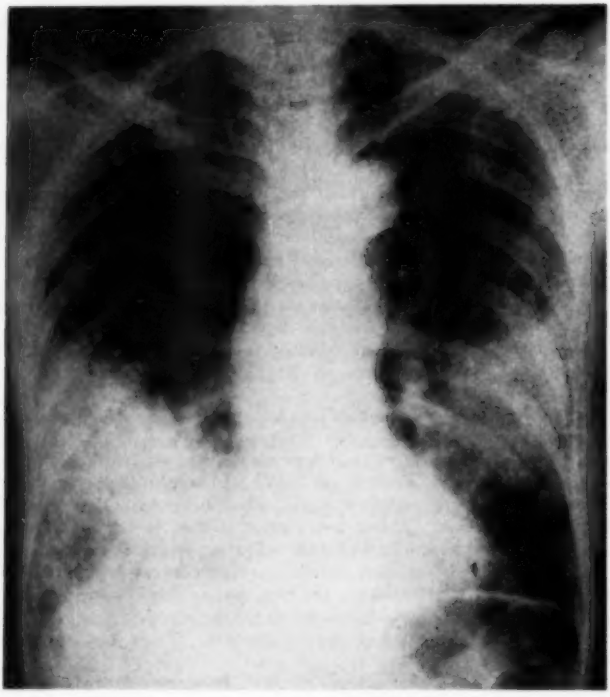

FIG. 1. Roentgenogram revealing extensive consolidation in both lower lobes caused by *Bacteroides funduliformis*.

lobe was the site of a diffuse, dense consolidation. The left lung had similar areas of consolidation, but these were largely in the lower lobe.

Multiple microscopic preparations of the lungs showed a confluent pneumonia. The alveoli in these areas were filled with a few large mononuclear phagocytic cells and leukocytes (figure 2).

Cultures of the lung at necropsy yielded *Bact. funduliformis* in pure cultures.

Case 3. A 52 year old Negro male was hospitalized on June 18, 1947, with the complaint of pain in the right lower chest and in the abdomen. Twelve days prior to admission, this patient had suffered a sudden onset of pain in the lower abdomen which gradually spread upward and became localized in the right lower chest. Shortly after the onset of the chest pain, the patient began to cough up thick, yellow, tenacious sputum which was blood-stained. On admission, right chest pain was severe and coughing was frequent. High fever had been present since the onset of this illness.

Examination revealed a temperature of 99.8° F., pulse 100, respirations 40, and blood pressure 155 mm. Hg systolic and 95 mm. diastolic. The general appearance was that of a well developed, well nourished Negro male showing limitation of motion of the right chest. Pulmonic examination revealed absent tactile fremitus on the right anteriorly and posteriorly, with decreased vocal fremitus and dullness to percussion

over the same areas. Cardiac examination disclosed a tachycardia of 120. Extreme tenderness was present in the right upper abdominal quadrant. The liver could be palpated 4 cm. below the right costal margin and was tender. There were no abdominal masses.

Upon admission, penicillin therapy was instituted, using 40,000 units intramuscularly every three hours. Also, sulfadiazine, in dosage of 2 gm. initially and then 1 gm. every four hours, was administered. In addition, the patient was given 500 c.c. of whole blood intravenously. A thoracentesis yielded 1,350 c.c. of purulent, very foul smelling fluid, and 60,000 units of penicillin were injected into the pleural cavity. The patient was transferred to thoracic surgery, and the following day a rib resection was carried out, with drainage of the empyema. At operation, a pus pocket was located which yielded 1,000 c.c. of seropurulent, fecal-smelling material. After this procedure, the patient slowly improved but continued to have a septic type of temperature, reaching 101° or 102° F. daily until four days prior to discharge. Hospitalization lasted 41 days.

Laboratory Findings: The white blood cell count was 26,050, with polymorphonuclear leukocytes 89 and lymphocytes 11; the hemoglobin was 9.5; urinalyses were essentially normal; two blood cultures were negative, but culture of the pleural fluid was positive for *Bact. funduliformis* in pure culture.

Comments: In all three of the cases discussed above, the portal of entry of the Bacteroides organisms was the respiratory tract. In the first case, septicemia developed and death resulted from multiple lung abscesses despite sulfathiazole and penicillin. While the clinical course in this prolonged case was steadily retrogressive, symptoms were surprisingly mild. *Bact. funduliformis* was isolated in pure culture from the blood on the eleventh day of hospitalization, and cultures of the blood, sputum and lungs at necropsy also yielded these organisms in pure culture.

The second patient displayed the most fulminating infection in this entire series. The period of illness was only three and one-half days, and necropsy revealed massive confluent bronchopneumonia from which *Bact. funduliformis* was obtained in pure culture. It is noteworthy that this was the only patient who appeared poorly nourished and poorly developed on admission; he was 64 years of age, and was the only one who "looked" critically ill.

In the last case, empyema followed pneumonia, and the empyemic material yielded pure *Bact. funduliformis* on culture. The empyemic fluid had a characteristic foul odor. In vitro sensitivity studies were carried out in another similar case of Bacteroides empyema which is not discussed and disclosed that aureomycin was an effective therapeutic agent, in contrast to streptomycin and penicillin (table 1). The usual pathologic finding in this group of cases was localized suppuration, which at times gave rise to septicemia or bacteremia with subsequent widespread involvement.

Bacteroides Infections Originating from the Gastrointestinal Tract

Six cases are included in this category. It is of interest that all of these patients were in critical condition. Four died and were subjected to nec-

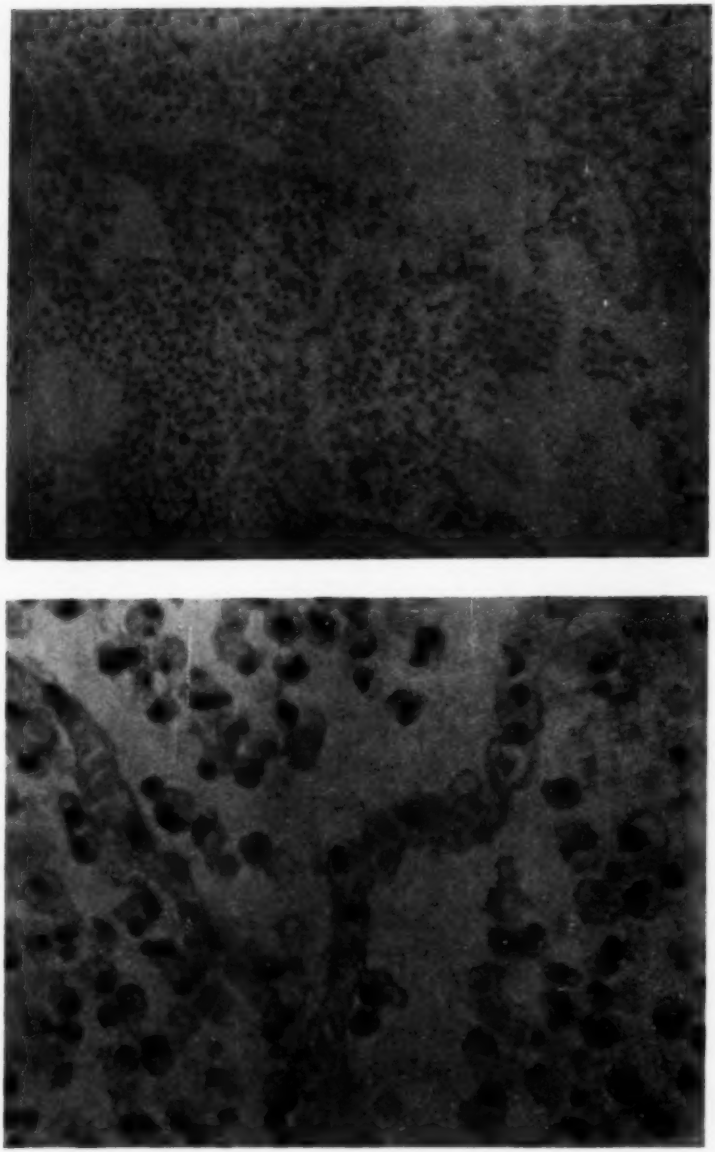

FIG. 2. Microscopic section under low and high power of lung tissue showing large mononuclear phagocytic cells and polymorphonuclear leukocytes.

TABLE I

Source of Bacteroides	Sensitivity Studies on Isolated Bacteroides Organisms									
	Aureomycin		Penicillin		Streptomycin		Sulfadiazine		Furacin	
	Inhibits	Does not Inhibit	Inhibits	Does not Inhibit	Inhibits	Does not Inhibit	Inhibits	Does not Inhibit	Inhibits	Does not Inhibit
Blood						75.0 α/c.c.				
Blood	13.0 α/c.c.			2.0 u./c.c.		250.0 α/c.c.		125.0 mg./c.c.		
Blood	12.0 α/c.c.			2.0 u./c.c.		250.0 α/c.c.		125.0 mg./c.c.		
Purulent material				10.0 u./c.c.						
Purulent material	2.0 α/c.c.			2.0 u./c.c.		250.0 α/c.c.				
Purulent material	10.0 α/c.c.			10.0 u./c.c.		125.0 α/c.c.				
Urine	14.0 α/c.c.			10.0 u./c.c.	125.0 α/c.c.					
Purulent material	12.0 α/c.c.			2.0 u./c.c.	75.0 α/c.c.					
Urine	10.0 α/c.c.			2.0 u./c.c.		125.0 α/c.c.				
Purulent material	20.0 α/c.c.			10.0 u./c.c.		125.0 α/c.c.				
Urine	40.0 α/c.c.	20.0 α/c.c.		10.0 u./c.c.		125.0 α/c.c.				
Purulent material	14.0 α/c.c.	12.0 α/c.c.		10.0 u./c.c.		125.0 α/c.c.				
Urine										1:2
Purulent material	12.5 α/c.c.	6.25 α/c.c.								

α/c.c. denotes micrograms per cubic centimeter.
u./c.c. denotes units per cubic centimeter.
mg./c.c. denotes milligrams per cubic centimeter.

ropsy. In all cases icterus was observed, and in five instances the presence of one or more hepatic abscesses was established at necropsy or by surgical procedures. *Bact. funduliformis* was isolated from the blood of three of these patients; all displayed a septic type of fever with an associated leukocytosis. The period of hospitalization varied from 23 to 71 days. The ages of these patients ranged from 11 to 71 years; four were males and two were females; five were Negroes and one was white. All appeared to be well nourished and well developed on admission. In only one case did the patient's general appearance correspond to the actual severity of his infection. During hospitalization, all of these patients were given massive quantities of various chemotherapeutic and antibiotic agents for prolonged periods, with very poor clinical response. Numerous operative procedures were carried out, with only limited success. One patient with Bacteroides septicemia included in this group responded dramatically to aureomycin and has been reported previously.[14]

Case 1. A 42 year old Negro female was hospitalized on April 2, 1945, with the complaints of nausea, vomiting, abdominal pain, chills, fever and constipation. A permanent colostomy had been performed one year previously because of an impassable rectal stricture due to lymphogranuloma venereum. The colostomy had functioned well until three weeks prior to admission. Since that time, there had been no actual passage of feces despite the repeated administration of cathartics. For two weeks prior to admission, the patient had noted nausea and vomiting following each attempt to eat or drink. During this same period, severe chills and high fever had occurred each evening. The nausea and vomiting were accompanied by severe, cramplike abdominal pains. There had been no anorexia, although little food or fluid had been retained since the onset of the illness.

Examination revealed temperature of 103° F., pulse 100, respirations 20, and blood pressure 138 mm. Hg systolic and 84 mm. diastolic. The general appearance was that of a well developed, moderately well nourished Negro female who showed definite evidence of dehydration. Abdominal examination revealed no distention and no involuntary rigidity, although some reflex rigidity and tenderness were present in the epigastric region. A colostomy was located in the left lower quadrant. There were no palpable abdominal masses. Rectal examination revealed an impassable stricture 4 cm. from the anus.

Upon admission, the patient was given glucose intravenously, and 48 hours after admission a soft diet was possible. Because of the continued septic temperature, sulfathiazole was administered. Three gm. orally were given initially, and then 1 gm. every four hours. On the tenth hospital day, it was observed that the patient's conjunctivae were icteric. Simultaneously, there appeared a cough productive of rusty sputum. Examination of the chest revealed decreased breath sounds, dullness to percussion and crepitant râles over the right lung base posteriorly. The patient became progressively more jaundiced and somewhat irrational; bilateral chest pain on coughing and deep inspiration was noted. The liver became tender and could be palpated 4 cm. below the right costal margin. Boardlike rigidity of the abdomen developed. Marked dyspnea and frequent vomiting ensued. In spite of repeated whole blood transfusions, intravenous fluids, nasal oxygen and Wangensteen suction, the patient died on the twenty-fourth day of hospitalization.

Laboratory Findings: The red blood cell count varied from 3,220,000 to 2,180,000; the hemoglobin from 9.5 gm. to less than 7.5; the white blood cell count from 15,500 to 32,100, with the differential on admission showing 98 per cent polymorphonuclear leukocytes and 2 per cent lymphocytes. Repeated urinalyses revealed 2 plus albumin. An icteric index on the tenth hospital day was reported as 20, and the non-protein-nitrogen on that date was 37 mg. per cent. Twelve days after admission, *Bact. funduliformis* was isolated from the blood in pure culture. A second positive blood culture for *Bact. funduliformis* was obtained on the day prior to death.

Necropsy Findings: The body was icteric, but well developed and well nourished. There were 2,000 c.c. of straw-colored fluid in the peritoneal cavity. The liver was enlarged, weighing 2,900 gm. On the anterior surface of its right lobe were several abscesses measuring 3 to 6 mm. in diameter. These abscesses contained a creamy, foul-smelling material. On the upper surface of the right lobe of the liver was a similar but much larger abscess. This abscess contained 1,800 c.c. of thin, greenish-gray material. On section of the liver, numerous other abscesses were found. Microscopic preparations of these abscesses showed the contents to be in many instances completely necrotic. In others, numerous polymorphonuclear leukocytes were found (figure 3). The spleen was increased in size, weighing 200 gm. Microscopically, it showed an increase of mononuclear elements in the splenic pulp.

Case 2. A 16 year old Negro male was hospitalized on October 2, 1947, in a semi-stuporous condition. No history could be obtained.

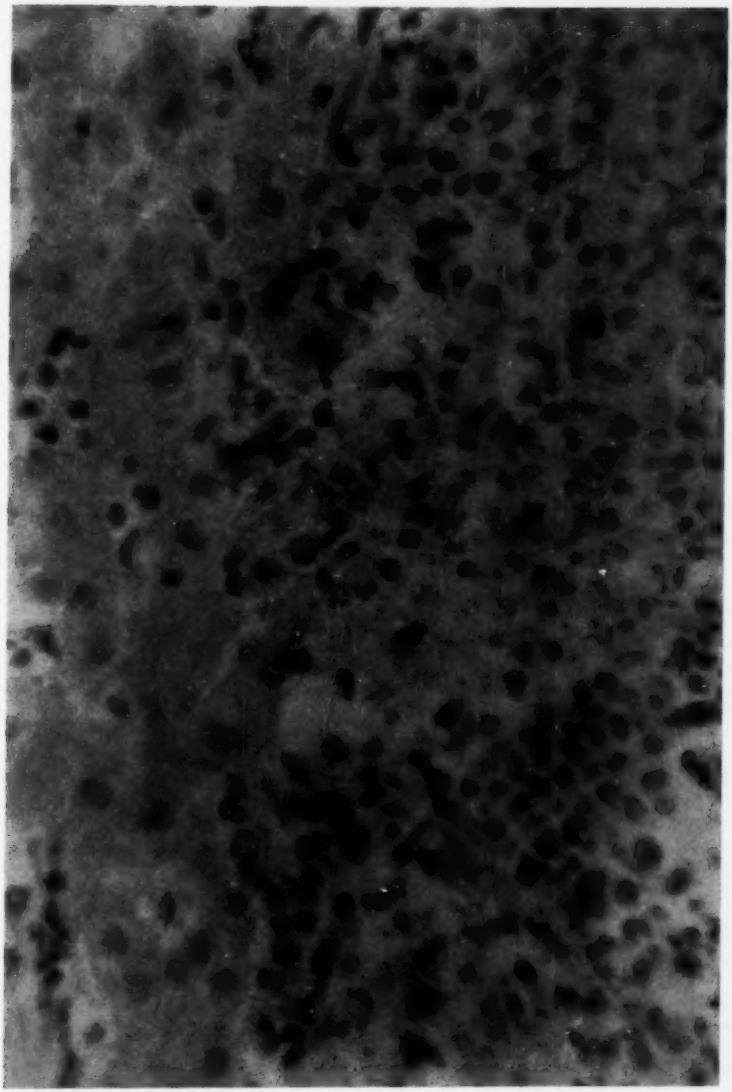

FIG. 3. Microscopic section under high power of hepatic abscess caused by *Bacteroides funduliformis.*

Examination revealed a temperature of 103.4° F., pulse 120, respirations 24, and blood pressure 100 mm. Hg systolic and 60 mm. diastolic. The patient was a well developed and well nourished Negro male who was quite restless, semi-stuporous and disoriented. A slight yellowish discoloration of the conjunctivae was noted. No cardiac abnormality was observed aside from a tachycardia. The abdomen was distended and tympanitic, with severe generalized pain being elicited on palpation and percussion; peristalsis was normal. Rectal examination revealed a tender, fluctuant mass in the pelvis. The entire right lower extremity and buttock were tense, shiny and swollen, with tenderness being especially marked over the anterior and lateral aspects of the right thigh. On pressure, gas was felt over the inguinal and femoral areas.

Immediately following hospitalization, the patient was given 50,000 units of penicillin intramuscularly every three hours, 200 mg. of streptomycin intramuscularly every four hours, and sulfadiazine in dosage of 4 gm. orally initially, and then 2 gm. every four hours; also, supportive intravenous glucose and whole blood were administered. The thigh was opened by multiple incisions on the medial, anterior and posterior aspects. Profuse, thin, cloudy, foul smelling pus was obtained, but no origin was found for the infection. This material yielded a pure culture of *Bact. funduliformis*.

Following drainage of the thigh, a septic temperature persisted, reaching 102° to 103° F. each day. Multiple blood transfusions were given, and Wangensteen suction was instituted to deflate the intestinal tract. However, the patient became progressively more jaundiced and irrational. Two days after admission he was returned to surgery, and a retroperitoneal abscess pointing through the sciatic notch into the right buttock was observed. A second abscess just posterior to the neck of the femur was also located. Multiple incisions were made above the right inguinal ligament as well as lateral and posterior to the rectum over the femoral neck to provide drainage. Following this procedure, the clinical picture remained unchanged. The wounds drained profusely and no improvement was noted. It became necessary to administer a general anesthetic in order to dress the lesions. On October 9, another abscess was observed in the right supraclavicular region; this was incised and drained. For about four days following this procedure, the patient showed some clinical improvement. He became rational and was able to eat a small amount of soft food. However, the temperature continued to be of a septic type, reaching 101° to 102° F. each day and, on October 16, the the patient again became irrational. Nevertheless, by the latter part of October the jaundice had essentially disappeared. On October 18 it became necessary to repass the Levine tube, and on October 22 Wangensteen suction was reinstituted. Three days later the patient developed profuse bleeding in the ischio-rectal cavity and passed into shock. He was removed to the operating room, and bleeding was controlled by packing the abscess cavity. On November 1, hemorrhage again occurred from the ischio-rectal region, and the patient again went into shock. Upon his being removed to surgery, a bleeding artery was located and ligated.

During hospitalization, two large decubitus ulcers developed. One ulcer was located over the sacrum and was about 10 cm. in width, penetrating to the bone; the other developed over the left hip and penetrated to the greater trochanter of the femur. It was decided to amputate the right leg and incise the hip joint for adequate drainage. Therefore, on November 13, a disarticulation of the right hip was carried out. Twenty-four hours later the patient died in shock.

Laboratory Findings: The red blood cell count varied from 3,850,000 to 1,100,000; the hemoglobin from 11.5 gm. to less than 4; the white blood cell count from 5,200 to 18,500, with the admission differential showing polymorphonuclear leukocytes 82, lymphocytes 14, and monocytes 4. A urinalysis on admission was within

normal limits. The total plasma protein varied from 6.0 to 4.7, non-protein-nitrogen from 37 to 56 mg. per cent, total serum bilirubin 0.8 to 12.3, with the indirect varying from 0.5 to 5.4, and the direct from 0.3 to 6.9. Cultures of the abscesses were positive for pure *Bact. funduliformis*, as was also a blood culture. Repeated throat and urine cultures were negative for Bacteroides. Streptomycin sensitivity studies with the Bacteroides organisms revealed no inhibition with 75 micrograms per cent (table 1).

Necropsy Findings: A large ulcerated area, 12 cm. in diameter, was present over the left hip, involving the skin and subcutaneous tissue and extending to the bone. A second ulceration, 2 cm. in diameter, was located over the crest of the left ilium. This lesion involved only the skin and adjoined a third ulceration, 10 cm. in diameter, which penetrated to the bone. On the posterior aspect of the left shoulder was a fourth ulceration, which measured 3 cm. in diameter and involved only the subcutaneous tissue. Multiple surgical incisions were present over the buttock and legs. Additional incisions were present over both arms and over the right inguinal ligament. Four hundred cubic centimeters of translucent fluid were present in the pericardial sac. The spleen weighed 195 gm. and was firm in consistency. The liver weighed 1,630 gm. and was yellow. Numerous focal hemorrhagic and necrotic areas were scattered throughout the liver substance. There was hemorrhage into the medulla and cortex of both adrenals. Both kidneys were large, flabby and multicolored.

Comments: The two cases discussed above illustrate the potential seriousness and the therapeutic problems of Bacteroides infections. Both of these patients died and were studied at necropsy. In each, the gastrointestinal tract was the portal of entry of the Bacteroides organisms; and in both, these bacteria were the primary pathogens and were obtained in pure culture. The blood stream was definitely invaded in these cases.

In the first case, *Bact. funduliformis* invaded the vascular system from the colon of a patient who had had a colostomy for the relief of an impassable rectal stricture. Death resulted from hepatic abscesses despite the use of sulfathiazole and general supportive therapy. Additional antibiotics were not available at that date (April, 1945).

In the second case, a perirectal infection proceeded to abscess formation which pointed through the sciatic notch into the right buttock and thigh, with resultant secondary cellulitis and arthritis. On admission, gas was noted, and it was assumed that a gas bacillus infection was present. However, culture yielded only *Bact. funduliformis*. Since this organism can produce gas, the clinical picture was entirely compatible with that caused by *Bact. funduliformis* alone. Surgical drainage and the simultaneous use of chemotherapeutic and antibiotic agents were ineffective. Hemorrhage occurred repeatedly from necrotic vessels; septicemia resulted with metastatic abscesses; toxemia developed, with profound changes in many organs.

Bacteroides Infections Originating in the Female Genital Tract

Thirteen cases are placed in this division, making it the largest category in the series. Six of these patients were in critical condition, with nine showing a persistent septic or spiking type of elevation. Two cases died

but necropsies could not be obtained. Hospitalization ranged from six to 86 days, with an average of over 30. The ages of the patients varied from 17 to 43 years; 12 were Negroes and one was white. In one of the fatal cases, *Bact. funduliformis* was isolated from the blood. Icterus was present in this patient, and the clinical course was characteristic of hepatic abscess. In all instances, a leukocytosis was present; all patients were well developed and well nourished, with only two persons appearing critically ill. Two infections in this category followed criminal abortions, and another two were associated with spontaneous abortions.

Case 1. A 32 year old Negro female was hospitalized with the complaints of lower abdominal pain, chills, fever, vomiting and vaginal discharge. For approximately nine months, this patient had noted a foul vaginal discharge. Ten days prior to admission, the onset of vaginal bleeding was noted. This was one week before the normal period. For three days there was little associated discomfort, but thereafter, intermittent vomiting, lower abdominal distention, lower abdominal pain, chills, fever and anorexia developed.

Examination revealed the temperature to be 101° F., pulse 92, respirations 20, and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. The general appearance was that of a well developed, well nourished Negro female in acute distress. The only significant physical findings were in the lower abdomen, which was slightly distended and extremely tender to palpation. No definite masses could be outlined but induration was noted. The uterus was quite tender to palpation, with the cul-de-sac bulging. Rectal examination also revealed bulging of the cul-de-sac. Colpocentesis yielded reddish-brown purulent material.

Upon admission the patient had been placed on penicillin, in dosage of 50,000 units intramuscularly initially and 30,000 units every three hours thereafter. Also, she was given 4 gm. of sulfadiazine initially and then 1 gm. every four hours by mouth. *Bact. funduliformis* in pure culture was obtained from the material recovered at colpocentesis.

The patient continued to have a septic type of temperature, with a daily peak of 101° to 103° F. in spite of penicillin and sulfadiazine. Therefore, 250 mg. of streptomycin were given intramuscularly every three hours. Also, whole blood transfusions and intravenous fluid were administered. Eight days after admission, jaundice was noted. An exploratory laparotomy was performed to provide extraperitoneal drainage for a probable right tubo-ovarian abscess. At operation, there was a diffuse inflammation of the pelvic peritoneum, with many adhesions, and several loops of small bowel were bound to the uterus. In the right adnexa was observed a thick-walled abscess from which 50 c.c. of very viscid, foul smelling, yellowish pus were removed. Following this procedure, the patient continued to have a daily temperature of about 101° F.

Two weeks following the exploratory laparotomy, a colpotomy was performed because of a fluctuant cul-de-sac mass, but no abscess cavity could be located. From this period until her discharge from the hospital on the fifty-second hospital day, the patient continued to have a daily temperature of about 101° F.

Following her discharge from the hospital, the patient was observed seven times in the Outpatient Department. There continued to be rather profuse, foul-smelling, greenish-white, purulent leukorrhea, and the patient showed a persistent weight loss. However, for the first few weeks there was subjective improvement. On her last visit to the Clinic, the patient was instructed to enter the hospital for further surgical procedures. She did not do so and died a short time thereafter.

Laboratory Findings: The red blood cell count varied from 3,630,000 to 6,030,000; hemoglobin from 8.5 gm. to 15.5; white blood cell count from 10,000 to 34,800. The white blood cell differential on admission revealed polymorphonuclears 93, lymphocytes 6, and monocytes 1. The corrected sedimentation rate (Wintrobe) was 36 mm. in one hour. A urinalysis revealed a trace of albumin, with 12 to 20 white blood cells per high power field following centrifugation. Repeated serum bilirubin examinations showed a variation in the 1 minute value of 8.0 to 0.8 and the total from 15.5 to 1.9. A 24 hour urine urobilinogen was 93.3 Ehrlich units. The total plasma protein ranged from 6.2 to 7.4 gm., with the albumin varying from 3.8 gm. to 3.6 and globulin from 2.4 gm. to 3.4. A culture of the material obtained from the original colpocentesis was positive for *Bact. funduliformis* in pure culture.

Case 2. A 21 year old Negro female was hospitalized on September 19, 1945, complaining of vomiting, pain in the right lower quadrant and in the right flank, and a mass in the right flank. The onset of the present illness had been one week prior to admission. Two years previously, this patient had suffered from severe right lower quadrant pain, with an associated foul, yellowish-green vaginal discharge, high fever and chills. She had been treated with sulfathiazole for several weeks without improvement, and had been compelled to remain in bed for more than a month. On January 2, 1945, she had been admitted to John Gaston Hospital. At that time, the foul, yellowish-green vaginal discharge was again noted, and on pelvic examination a fistulous tract was found in the vaginal vault, about 2 cm. from the cervix. This was believed to be a ureterovaginal fistula. After six weeks of observation and symptomatic therapy, the patient was subjected to an exploratory laparotomy. Just on the inside of the brim of the pelvis, medial to the iliac vessels, was an elongated, slightly indurated, retroperitoneal mass lying beside the right psoas muscle. This mass was left unopened, and the patient was released on the fourteenth postoperative day, though the discharge from the vagina continued unaltered. A culture from the vaginal discharge obtained shortly after admission had been found to be positive for *Bact. funduliformis.*

Five months later, the patient was re-admitted to John Gaston Hospital with pain in the right lower quadrant and in the right flank, nausea and vomiting. The yellowish-green, foul leukorrhea was still present, as was the ureterovaginal fistula. The patient was given 3 gm. of sulfathiazole initially by mouth, and then 1 gm. every four hours. A low grade elevation persisted throughout hospitalization, and the patient was discharged after one month showing little clinical change.

Examination on the final admission, on September 19, 1945, revealed temperature 102.4° F., pulse 140, respirations 40, and blood pressure 100 mg. Hg systolic and 70 mm. diastolic. The general appearance was that of a well developed and well nourished but acutely ill Negro female. Exquisite generalized abdominal tenderness was present, and a tender palpable mass was located in the right flank. Incision and drainage of the cul-de-sac was attempted, but only a small amount of foul-smelling greenish material was obtained. This material yielded *Bact. funduliformis* in pure culture. Therapy consisted of intravenous sulfadiazine, glucose and whole blood. Wangensteen suction was instituted and nasal oxygen administered. However, the patient died on the fourth hospital day, having displayed a persistent septic type of temperature which reached 105° to 106° F. each day.

The sulfadiazine blood level on the day prior to death was 7.1 mg. per cent. On all three admissions a leukocytosis with a shift to the left was present. The hemoglobin was 10 gm. per cent on each admission.

Comments: In the two cases described above, there was a prolonged, toxic and debilitating clinical course. Response to operative procedures,

antibiotics and chemotherapeutic agents was uniformly poor. The possible significance of Bacteroides in chronic, resistant pelvic infections must be emphasized. Four unreported cases in this series also stress the potential importance of these organisms in puerperal infection, as two Bacteroides infections followed spontaneous abortions, and an additional two developed after criminal abortions. While necropsy examination was not possible in any of the cases in this group, the clinical picture was that of a pyogenic infection tending to the formation of abscesses.

Bacteroides Infections Originating in the Urinary System

Seven cases are included in this category. It is noteworthy that all of these patients were females and that none was seriously ill from the Bacteroides infection per se. One patient died and was autopsied, with the cause of death established as a neuroblastoma of the left adrenal which had invaded the left kidney and had metastasized widely. In no case in this group was septicemia demonstrated, and in only one case was there a septic type of fever with associated leukocytosis. In this instance, the primary disease entity was gonorrheal arthritis.

This is the only group in which white patients constituted a significant proportion: four were Negro and three were white. In four cases, Bacteroides were obtained in pure culture from catheterized urine specimens. In only two, and possibly three, instances were Bacteroides organisms of possible clinical importance.

This group of cases constitutes the most ill-defined and clinically insignificant category in the series. In all of these cases, the Bacteroides infection appeared to be limited to the urologic tract, with no systemic effects being noted. The potential importance of this category, however, is obvious, as septicemia could arise as well from the urinary tract as from the respiratory, intestinal, genital or auditory systems, if the proper predisposing factors (surgery, trauma, malignancy, etc.) were present. Only one case is reviewed.

A 41 year old Negro female was seen in the Outpatient Department because of gross painless hematuria which had begun four days previously and had become a painless terminal hematuria. Coincident with the onset of the urologic condition, a severe sore throat had been noted. This disappeared shortly. There was no history of back pain.

Cystoscopic examination revealed only a small number of petechiae about both ureteral orifices and hyperemia of the trigonal area. There was no obstruction to the passage of ureteral catheters. Retrograde pyelograms were normal.

It was decided to treat this patient for trigonitis with Furacin if hematuria recurred. Because of the intervention of menstruation, the patient was not observed again until March 21, when she returned to the clinic complaining of dizziness and brown urine. A catheterized urine specimen disclosed 3 plus albumin and red blood cells too numerous to count. Pending the results of culture of a catheterized urine specimen, 4 c.c. of Furacin were instilled into the bladder on three occasions at approximately two day intervals.

The patient's last visit to the clinic was on March 28, 1950, at which time she complained of extreme weakness, "nervousness" and nocturnal urinary incontinence. Urinalysis revealed 2 plus albumin and red blood cells too numerous to count. *Bact. funduliformis* were obtained in pure culture from the catheterized urine.

Inasmuch as the patient failed to return to the Clinic, additional information is not available. The only in vitro studies carried out in this case disclosed that a concentration of 1:2 Furacin did not inhibit the Bacteroides organisms.

Comments: In this case, adequate follow-up studies were impossible. The Bacteroides organisms could not be definitely established as pathogenic in this instance (table 1).

Cutaneous Bacteroides Infections

Only one case of this type of Bacteroides infection was observed at John Gaston Hospital during the past five years. This patient was not in critical condition, and hospitalization was brief.

A 21 year old Negro male was hospitalized on August 30, 1945, complaining of pain and swelling in the left shoulder area. Three weeks before admission, this patient noted a sharp pain in the left scapular region. The following night he noted a tender, inflamed swelling in this area. Six months previously he had been stabbed in this location, but healing had been uneventful.

Examination revealed a temperature of 99.6° F., pulse 80, respirations 20, and blood pressure 130 mm. Hg systolic and 80 mm. diastolic. Over the left scapular area was a hot, tender mass about the size of a small grapefruit.

The patient was given 10,000 units of penicillin intramuscularly every three hours, together with 1 gm. of sulfadiazine every four hours orally. However, a septic temperature reaching 101° to 102° F. each day persisted until the lesion was incised. A large amount of grayish, foul-smelling, purulent material was obtained which yielded anaerobic nonhemolytic streptococci and Bacteroides on culture. The patient became afebrile on the sixth hospital day and was discharged four days later.

The red blood cell count was 5,550,000; hemoglobin was 16 gm.; white blood count was 7,100, with polymorphonuclear leukocytes 71, lymphocytes 28, and atypical cells 1. A urinalysis was negative.

Bacteroides Infections Originating in the Auditory System

Only two cases were observed in this category. Both were Negro male infants who were critically ill; both had initial otitis media, with subsequent septicemia and severe complications. One recovered after a prolonged illness, but the other died and was autopsied.

Case 1. A seven month old Negro male infant was hospitalized on February 2, 1950, but died five minutes later. The child had been well until one week previously, when a purulent drainage from the right ear was noted. The infant did not appear seriously ill until 48 hours prior to admission, when a high temperature developed.

A superficial examination in the Receiving Ward disclosed a well developed, very dehydrated Negro male infant who did not feel feverish, was extremely icteric, had no lymphadenopathy or petechiae. The right pupil was dilated and would not react to light. Profuse purulent drainage from the right ear was observed. The child was obviously moribund and died before reaching the ward.

Necropsy Findings: The skin and mucous membranes were icteric and pale. There was a purulent right otitis media, with the inflammatory process causing thickening of the mucosa of the right middle ear and destruction of bony structures. The periosteal surface was jagged and irregular, and many spicules of dead bone were present within the cavity of the right middle ear.

A moderate but widely disseminated inflammatory reaction involved the leptomeninges covering the cerebrum and cerebellum. This reaction was most marked in the pia-arachnoid which enclosed the tip of the right temporal lobe. The cellular infiltrate in this area was composed primarily of polymorphonuclear leukocytes, fibrin, fluid and cellular debris (figure 4). In other areas, mononuclear leukocytes predominated. The bone marrow was extremely hyperplastic and contained large numbers of nucleated erythrocytic and early myeloid cells.

Culture at necropsy of the right middle ear, cerebrospinal fluid and the heart blood yielded a pure culture of *Bact. funduliformis.*

Case 2. A six month old Negro male infant was hospitalized with the history of cough and rhinitis for three weeks and purulent drainage from the right ear for two weeks. He had been given an undetermined amount of sulfadiazine two weeks prior to hospitalization, without improvement. High fever had been noted for one week; three days before admission to the hospital, swelling, redness, tenderness and pain on motion of the right ankle had been noted. Similar involvement of the left wrist was observed on the day of admission.

Examination revealed temperature of 102° F., pulse 110, respirations 22. The right ear was filled with, and was draining, a whitish purulent material. The left drum was reddened, with decreased light reflex but without bulging. There was no discharge and no pain on manipulation of the left ear. There was no inflammation of the pharynx. Marked swelling, heat, redness and tenderness of the right ankle were noted. A similar, but less, involvement of the left wrist was observed. Cervical, axillary and inguinal lymph nodes were enlarged and palpable.

Immediately after admission, aqueous penicillin was begun, in dosage of 100,000 units intramuscularly initially and then 10,000 units every three hours; also, sulfadiazine was given in the following amounts: 7.5 gr. (0.5 gm.) initially and then 2.5 gr. (0.167 gm.) every four hours. This medication was continued until discharge from the hospital. After five days, the patient became afebrile and was discharged on the eighth hospital day.

On this admission, the white blood cell count was 19,800, with polymorphonuclears 38, lymphocytes 61, and eosinophiles 1. The hemoglobin was 9, the red blood cell count 4,610,000. A urinalysis revealed 1 plus albumin. A blood culture was positive for pure *Bact. funduliformis.*

Roentgenograms of the right ankle and left wrist revealed no bone abnormality.

This infant was re-hospitalized 10 days later with a history of high fever and bilateral earache for five days. Lethargy had been noted for four days; a generalized convulsion occurred on the day of admission.

Examination on re-admission revealed temperature of 104.6° F., pulse 200, and respirations 55. The general appearance was that of a well developed and well nourished Negro infant who appeared acutely ill. Nuchal rigidity was present; bilateral otitis media was noted; hyperemia of the mucous membranes of the nose and pharynx was observed; respiration was rapid and a tachycardia was present. Brudzinski's reflex and Kernig's sign were positive.

The following therapeutic regimen was begun: 250,000 units of aqueous penicillin intramuscularly every three hours, streptomycin, 120 mg. orally every eight hours, and sulfadiazine, 1 gm. initially by mouth and then 1/3 gm. every four hours. Supportive therapy included nasal oxygen and vitamins; convulsions were controlled with intramuscular sodium amytal.

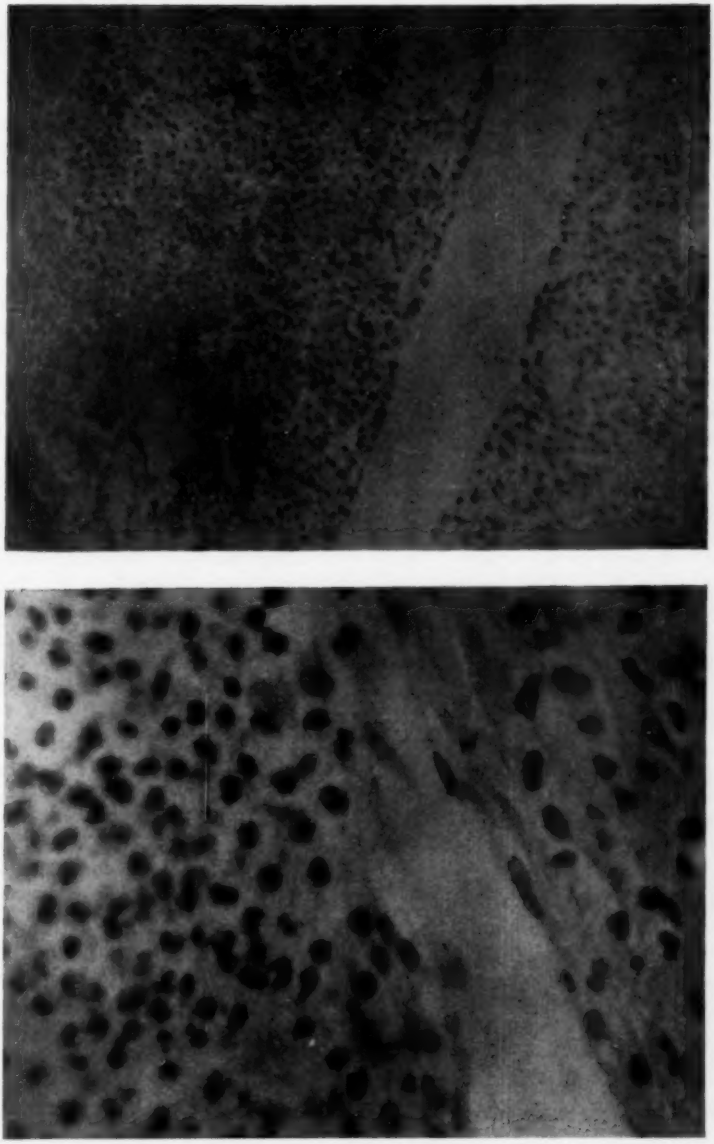

FIG. 4. Microscopic section under low and high power of meningitis caused by *Bacteroides funduliformis*.

After three days the septic fever was replaced by a low grade elevation, but treatment was continued for 53 days because of a persistent leukocytosis in the peripheral blood and derangement of spinal fluid elements—continued elevation of cells and protein. When the infant was discharged it was believed that there was impairment of hearing, possibly secondary to streptomycin.

The cerebrospinal fluid showed the following variation: total white blood cells, 203 to 7, with polymorphonuclear leukocytes from 71 to 2 per cent, lymphocytes from 29 to 98 per cent; protein from 140 to 24 mg. per cent; chloride (as NaCl) from 700 to 730 mg. per cent; sugar from 16 to 71 mg. per cent. The total white blood count in the peripheral blood varied from 20,500 to 12,600. Repeated cultures of the spinal fluid were negative; first and second strength intradermal tuberculin tests were negative.

Comments: In both of the cases presented above, Bacteroides were obtained in pure culture and were pathogenic, resulting in death in one instance and a prolonged serious illness in the other. The disease process in both cases originated as an otitis media and progressed to septicemia and meningitis. Icterus in the first patient resulted from hemolytic anemia. The possible significance of Bacteroides in otitis media and meningitis must be stressed.

Discussion

Bacteroides infections are regarded as exotic and rare conditions by the vast majority of physicians. Many have never heard of these organisms. Yet 35 cases of Bacteroides-caused infections were observed at the John Gaston Hospital during the past five years. Twenty-one of these patients were in critical condition and 11 died. Bacteroides organisms were the primary cause of death in nine of these cases and were secondary invaders in patients dying of malignancy in the other two instances. Necropsies were performed on nine of these patients.

Despite the evidence of Thompson and his associates [2] that Bacteroides organisms can be pathogenic, many physicians believe that they are merely contaminants and are of little clinical significance except in extremely debilitated patients in extremis. However, the average age of patients in this series with Bacteroides septicemia was 27 years, and only one was above the age of 42. In eight cases of septicemia the average period of hospitalization was 43 days, yet a positive culture of Bacteroides was obtained on the first to the twelfth hospital days, with the average being on the seventh. It is significant that a pure culture of Bacteroides was obtained in all of these cases, though in one case *Streptococcus fecalis* was also isolated from the blood stream at other times. Thirty-one of the patients in this series were regarded as being well nourished and well developed at the time of hospitalization.

The ages of patients ranged from seven months to 71 years; 24 were females and 11 were males; 30 were Negroes and five were white. The preponderance of female patients resulted from the large number with pelvic infections. Also, all of the Bacteroides urinary tract infections occurred in females. It is our opinion that the apparently increased susceptibility of

Negroes in this series to Bacteroides organisms is explained by the fact that over 70 per cent of the patients in the John Gaston Hospital are Negroes.

An interesting clinical observation in the majority of cases was the fact that the "look" of the patient often did not correspond to the actual seriousness of the infection. While patients often exhibited a very high elevation of temperature (for example, 106° F.), with a marked leukocytosis, their symptoms were frequently minimal. This was noted in three cases of septicemia, two of whom died. The usual clinical picture was that of a pyogenic infection, with the dominating symptoms being determined by the portal of entry: respiratory tract, gastrointestinal tract, genitourinary system, auditory system or skin. The characteristic pathologic lesion was that of localized suppuration similar to that caused by staphylococci, which at times extended to invade the blood stream, with subsequent bacteremia or septicemia and metastatic abscess formation. When the latter occurred, the patient became critically ill and the prognosis grave.

In 22 cases, Bacteroides were obtained in pure culture from blood, purulent material, urine and cerebrospinal fluid; in 10 instances, these organisms were associated with one to three other bacteria, and in three cases Bacteroides were obtained alone on one occasion but associated with another organism at another period. In seven instances, Bacteroides were isolated in association with *Streptococcus anaerobius;* in three cases, with *Streptococcus faecalis;* in three cases, with *Streptococcus pyogenes;* and in one case, *Micrococcus pyogenes* var. *aureus, Escherichia coli, Aerobacter aerogenes* and diphtheroids.

In view of the prolonged, debilitating and often fatal outcome of many Bacteroides infections, early diagnosis and appropriate treatment are essential. In vitro sensitivity studies were carried out with Bacteroides organisms isolated in 14 cases. Using streptomycin, sulfadiazine, penicillin and aureomycin, the latter was found to be by far the most effective (table 1). A proper therapeutic regimen in Bacteroides infections should include adequate amounts of aureomycin, maintenance of nutrition, preservation of proper electrolyte balance by the appropriate use of intravenous fluids and whole blood, as well as indicated surgical procedures for drainage of purulent material. When the oral route of administration cannot be utilized, intravenous aureomycin should be given. In this manner, we have successfully treated two patients with *Bact. funduliformis* septicemia.[14]

The importance of Bacteroides organisms in infections of undetermined etiology that do not respond to usual therapeutic measures must be emphasized. Many patients in this series received vast amounts of all available chemotherapeutic and antibiotic agents with little or no clinical improvement. This was noteworthy in Bacteroides-caused pelvic infections. The significance of Bacteroides in pneumonia, empyema, liver abscess and urinary infections must be stressed. Improved laboratory facilities and a greater awareness on the part of physicians should lead to increasing recognition of the importance of Bacteroides infections in man.

Summary

Thirty-five cases of Bacteroides infection observed over a period of five years have been reviewed. These have been classified on the basis of the portal of entry of the Bacteroides organisms. An attempt has been made to correlate the pathogenesis, clinical picture, prognosis and therapy in these cases. In vitro and in vivo studies indicate that aureomycin may be the therapeutic agent of choice in these infections.

It is believed that the importance of Bacteroides infections has been grossly underestimated.

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THERAPY OF GONOCOCCAL ARTHRITIS *

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Therapeutic results in gonococcal arthritis have improved materially since the introduction of antibiotic agents. Detailed information regarding the efficacy of this therapy is sufficiently meager to justify the addition of results obtained in a recent series of cases.

Evaluation of any therapeutic procedure necessitates an understanding of the natural course of the disease being studied. Untreated genital gonorrhea undergoes spontaneous cure in 17 per cent of cases.[1] Key [2] has stated that gonorrheal arthritis is, in many instances, a self-limited disease. In untreated patients, the incidence of complications such as prostatitis, epididymitis, salpingitis and arthritis is high, being 37.9 per cent in the report by Cohn, Kornblith and Steer.[1] In World War I in Germany, 10 per cent of cases of gonococcal urethritis developed arthritis. A subsequent series reported a lower incidence, namely, 1 to 5 per cent.[3] Spink and Keefer [4] studied 70 cases of gonococcal arthritis treated in the prechemotherapy era. Their cases were divided into three approximately equal groups, depending on the severity of the process: (1) milder cases, treated symptomatically; (2) more severe cases, treated by joint aspirations, and (3) severe cases with purulent joint effusions, treated by open drainage. In the first group, 75 per cent of the patients made complete recoveries without any residual symptoms. Of the second group, 48 per cent recovered complete joint function, while only 15 per cent of the third group recovered completely. The percentage of positive joint cultures was 8 per cent in group II and 75 per cent in group III. A total of 17 of their 70 patients (24 per cent) was proved to have positive joint fluid cultures. They observed that sterile joint effusions could persist for months without causing joint destruction, whereas infected fluids often produced cartilaginous damage in a very few weeks. Thirty-five of their 70 patients (50 per cent) made complete recoveries without any residual signs or symptoms.

The diagnosis of gonococcal arthritis is based on the following criteria:

1. History of genitourinary gonococcal infection and/or exposure.
2. Positive local smear and/or culture.
3. Clinical course of the disease.
4. Positive gonococcus complement fixation test in serum and/or joint fluid.
5. Positive joint culture.

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The presence of a positive culture is usually required to consider a diagnosis "proved," diagnoses based on other criteria being considered "presumptive." It is suggested that a sixth criterion be added, even though there are some exceptions:

6. Response to penicillin therapy.

The onset of gonococcal arthritis is characterized by an acute migratory polyarthritis, frequently very similar to that observed in acute rheumatic fever. This phase may well represent a hypersensitivity reaction to the gonococcal products, as suggested by Ralston,[5] who produced an acute polyarthritis in horses by injecting gonococcal toxins and autolysates intravenously. Two to five days after onset, migratory symptoms subside and one or more joints develop persistent signs of acute inflammation.[2, 6, 7] Harkness [8] reported that 83 per cent of 336 cases of gonococcal arthritis were polyarthritic in nature. As previously pointed out, approximately two-thirds of the persistently inflamed joints may develop a significant effusion and one-fourth a positive culture.

The gonococcus complement fixation test is a valuable diagnostic aid, having been found positive in 80 to 90 per cent of presumptive or proved cases of gonococcal arthritis.[8, 9, 10] Warren, Hinton and Bauer [9] found the test positive in 91.7 per cent of cases with a presumptive or proved diagnosis, whereas the test was positive in 8.7 per cent of cases with non-gonococcal arthritis, and negative in all cases without evidence of joint disease. These authors conclude that negative tests reported in gonococcal arthritis are due to the following reasons:

1. Tests made on a given patient are insufficient in number.
2. Tests are not made in recovery phase.
3. Tests are performed after complete cure (i.e., too late).
4. Gonococcal fixation antigen is not specific for the patient's strain of antibody.

Admittedly, there is no more absolute criterion for the establishment of a diagnosis of gonococcal arthritis than the isolation of the gonococcus from joint fluid. However, if one accepts the work of Spink and Keefer,[4] this finding is present in only 24 per cent of cases of this disease. It seems somewhat unreasonable to brand cases with the dubious term "presumptive" just because a positive culture was not present. This seems particularly unjustified when one notes a dramatic response to penicillin therapy. It is felt that if criteria 1 and/or 2, 3 and 4 are combined with a definite response to penicillin, the diagnosis should be considered "proved." Certainly the exactness of this method far exceeds the standards for diagnosis of many other medical conditions, e.g., rheumatic fever and rheumatoid arthritis. Post-gonococcal rheumatoid arthritis may be identified by the lack of response to penicillin therapy. A dramatic response to penicillin was seen in 27 of our 30 cases (90 per cent).

Data such as fever, pulse, leukocyte count, sedimentation rate, roentgen-ray findings and synovial fluid cytology and chemistry are so variable as to be of no value as diagnostic aids.

Specific therapeutic agents against the gonococcus have included artificial fever, sulfonamides and antibiotic therapy. Each in turn has rendered its predecessor more or less obsolete.

The introduction of fever therapy marked a great step forward in the treatment of gonorrheal infections. The rationale of this mode of therapy was based on the susceptibility of the gonococcus to temperatures readily produced in and tolerated by man. Carpenter et al.[11] found that 99 per cent of gonococcal strains were destroyed in four to five hours at 41° C. (105.8° F.). The same percentage was killed in two hours at 41.5° C. (106.7° F.) to 42° C. (107.6° F.) There is a good correlation between the thermal death time of an organism and the amount of fever therapy required to kill that organism in vivo, but this correlation is not absolute, as host factors of resistance undoubtedly play an additional rôle in recovery. Results in fever therapy of gonococcal arthritis have been good, approximately 75 per cent [6, 12, 13] of patients being cured by this form of therapy.

Sulfonamide therapy provided an equally effective [1, 14] and much simpler method of treating this disease. With the introduction of sulfonamides, the incidence of gonococcal arthritis following genitourinary gonorrhea declined markedly, to 0.1 to 0.3 per cent.[15] However, in the past few years there have been numerous reports [16, 17, 18, 19] of sulfonamide-resistant gonococcus infections, indicating a decline in efficacy of this form of therapy.

There have been a number of favorable reports on the use of penicillin in the therapy of gonococcal arthritis.[6, 20, 21, 22, 23, 24] One of the most comprehensive studies is that of Spitzer and Steinbrocker,[25] who reported 28 cases of gonococcal arthritis treated with penicillin. They reported prompt "bacteriological cure" in every case. There was a rapid subsidence of fever, pain and swelling, and there were no evidences of progression, newly involved joints or reactivation of the initial or local site of infection after penicillin therapy was begun. They classed as treatment failures five cases with residual joint signs or symptoms. Miller and Boor [26] report that penicillin protects mice against the lethal action of gonococcal endotoxins; hence, this agent may be of value not only as a bacteriostatic agent but also as an "antitoxic" agent. This seems especially important when patients are treated in the so-called "allergic" phase of the disease.

Diffusion of penicillin into the joint spaces occurs readily, and synovial and blood concentrations approximate each other one hour after therapy is instituted.[27] In addition, concentrations of penicillin in joint fluid decline more gradually than those in the serum.[27, 28]

Numerous reports [29, 30, 31, 32, 33] have denied the presence of natural resistance of the gonococcus to penicillin, either in vitro or in vivo. Acquired resistance of the gonococcus to penicillin has been demonstrated [34, 35, 36] by

subculturing the gonococcus in increasing concentrations of penicillin. This is accomplished, however, far less readily than with sulfonamide drugs.

Up to this time, there are only four reported cases of gonococcal infections with both in vitro and in vivo resistance to penicillin.[37] These patients were originally treated with small and intermittent doses of penicillin, and the organisms may therefore have acquired this resistance. Penicillin dosages may have been inadequate in three of the four cases. In each instance, the patient was cured by fever therapy.

Recently, aureomycin [38, 39, 40, 41, 42, 43, 44] and streptomycin [42, 44, 45, 46] have been found efficacious in the treatment of gonococcal urethritis. It has been suggested that these drugs be used for the rare cases of penicillin-resistant gonococcal infections.

The present report is based on an analysis of 30 cases of gonococcal arthritis treated with penicillin and other agents at St. Louis City Hospital, Homer G. Phillips Hospital and Barnes Hospital from 1943 to 1950. Cases showing clinical penicillin resistance will be discussed in detail.

Details regarding each of the 30 patients are presented in table 1. It will be seen that 28 of the 30 patients had a definite history of genitourinary gonorrhea. The two without such history were two females of "questionable character." Seventeen patients had a positive urethral or cervical smear and/or culture; in eight cases these tests were negative and in five they were not performed (in four instances due to lack of secretions). Six patients with negative local bacteriologic findings had had sulfonamide or antibiotic therapy prior to admission. Thirteen patients developed arthritis in spite of previous sulfonamide, penicillin or combined therapy. The period from onset of genitourinary infection to the development of joint symptoms varied from two days to 23 years. Joint manifestations existed from two to 120 days prior to the institution of therapy. All but six patients had migratory joint involvement at the onset. Only four patients (13 per cent) developed persistent mono-arthritis; the remaining 26 (87 per cent) had two or more involved joints. Admission temperatures varied from normal to 104.6° F. (40.4° C.). White blood cell counts varied from 4,500 to 20,500/mm.^{3} and sedimentation rates ranged from normal to very rapid. Temperatures, leukocyte counts and sedimentation rates served as valuable indices of the severity of the infection. Gonococci were found in the joints in cases 1 through 5. In four instances their presence was proved by culture, and in the fifth by a positive smear.

The gonococcus complement fixation test was positive in 14 cases at admission, and an additional 10 patients developed this reaction in subsequent tests. In four cases, positive gonococcal fixation tests were not obtained, possibly because the test was not repeated in convalescence. In two instances the test was not performed at all. Gonococcus complement fixation tests were performed on six synovial fluids. Three of these were positive, as was the blood test in each of these individuals.

TABLE I

Case No.	Race Age Sex	Genitourinary Infections			Interval[2]	Arthritis			Joint Fluid Sm./Cult.	Bl. G.C. Fix.	Pen.[5]	Results	
		History	Sm./Cult.	Treatment[1]		Duration[3]	M	Pa[4]				X-Ray	Clinical
1	Wh. 26 M	+	0 0	P	27 d.	5	+	+	− +	− → +	15.5	+	See text.
2	Col. 19 F	+	0 −	0	5 mo.	19	+	+	− +	−	4.5 (0.01)	+	Residual stiff finger, otherwise well.
3	Col. 54 F	?	− −	S	7 d.	14	+	+	− +	+	16.1 (0.07)	−	Mod. flexion contracture of knee.
4	Wh. 23 F	+	+ −	S	?	36	−	−	− +	−	.760	−	Cure. Sulfa and fever therapy also given.
5	Wh. 19 F	+	+ −	?	5 d.	4	−	+	+ −	− → +	2.55	−	Cure.
6	Wh. 28 F	+	− +	P	12 mo.	5	+	+	0	− → +	4.0	−	Sl. residual stiffness.
7	Col. 32 M	+	+ +	0	15 y.	4	+	+	0	− → +	8.0	−	Sl. residual stiffness.
8	Wh. 54 M	+	− +	0	10 d.	26	+	+	0	± → +	8.1	−	Cure.
9	Wh. 24 F	+	+ +	0	?	10	+	+	0	− → +	2.4	−	Cure.
10	Wh. 51 M	+	+ +	0	3 d.	4	−	−	− −	− → +	5.5	−	Sl. stiffness.
11	Wh. 20 F	?	− −	S	?	31	+	+	0	− → +	1.2	−	Sl. stiffness.
12	Wh. 35 M	+	+ +	S P	14 d.	16	+	+	− −	− → +	10.97	−	See text.
13	Wh. 50 M	+	0	0	?	14	+	+	0	− → +	1.87	−	Cure.
14	Wh. 23 F	+	+ −	0	11 d.	4	+	+	0	+	4.0	−	Cure.

[1] S—Sulfonamide. P—Penicillin.
[2] Interval refers to period between onset of genitourinary infection and joint symptoms, expressed as: d—days, mo.—months, y—years.
[3] Duration of joint symptoms in days before institution of penicillin therapy.
[4] M—Migratory. Pa—Polyarticular.
[5] Figures represent total parenteral penicillin dosages in millions of units. Figures in parentheses represent total amount of penicillin given intraarticularly.

TABLE I (*Continued*)

Case No.	Race Age Sex	Genitourinary Infections			Interval[3]	Arthritis		Joint Fluid Sm./Cult.	Bl. G.C. Fix.	Pen.[5]	Results	
		History	Sm./Cult.	Treatment[1]		Duration[2]	M Pa[4]				X-Ray	Clinical
15	Wh. 44 M	+	0	0	23 y.	2	− −	− −	+	4.21	−	Sl. residual tenderness.
16	Wh. 34 F	?	+ +	0	?	7	+ +	0	−	3.99	−	Cure.
17	Wh. 26 F	+	− −	0	2 mo.	9	+ +	− −	+	5.0	−	Cure.
18	Wh. 42 M	+	− −	S	2 d.	21	+ +	0	+	4.62	−	Cure. Keratoderma cleared up.
19	Wh. 24 F	+	+ −	S P	?	22	− +	0	0	1.98	−	Cure. Also given sulfonamide.
20	Wh. 28 M	+	+ +	P	2 d.	23	+ +	− −	+	28.04 (0.320)	−	See text.
21	Wh. 19 F	+	− −	0	9 d.	9	+ +	− −	+	2.71	−	Cure.
22	Wh. 22 F	+	− −	0	?	4	+ +	0	+	2.0	−	Cure.
23	Wh. 27 F	+	+ +	0	?	23	+ +	0	+	3.84	−	Cure.
24	Wh. 23 M	+	0	P	14 d.	21	+ +	− −	+	3.46	−	Cure.
25	Wh. 18 F	+	+ +	0	?	14	+ +	0	+	0.3	0	Cure.
26	Col. 28 F	+	+ +	0	21 d.	2	+ +	0	+	4.8	−	Cure.
27	Col. 43 M	+	0 −	P	21 d.	120	+ +	0	+	3.2	+	Osteoporosis. Symptoms relieved.
28	Col. 19 F	+	0	P ?	9 mo.	12	+ +	− −	+	4.1 (0.01)	−	Cure.
29	Wh. 19 F	+	+ −	P	11 d.	4	− −	0	0	1.4	0	Cure.
30	Wh. 53 M	+	+ 0	0	2 d.	2	+ +	0	−	1.38	0	Cure.

Roentgenograms revealed joint destruction in only two instances, and in each of these a positive joint culture was obtained.

Electrocardiograms were taken in 10 of the 30 cases. These were all within normal limits. In view of a report [47] of abnormal electrocardiographic findings in gonococcal arthritis, it is suggested that routine electrocardiograms be done on all gonococcal arthritis patients to evaluate this procedure further.

Penicillin was administered to each patient in the series. The total dosage ranged from 0.3 to 28.04 million units, the average total dose being 5.5 million units. Four patients received supplementary intraarticular penicillin. Five patients received additional types of therapy, including sulfonamides, fever therapy, aureomycin and streptomycin. Combined aureomycin and streptomycin therapy was used in the treatment of one of our cases of penicillin-resistant gonococcal arthritis. To our knowledge, this is the first reported case of a penicillin-resistant gonococcal arthritis treated with these drugs.

In general, results in penicillin therapy were satisfactory, but three cases presenting apparent penicillin-resistance will be discussed in detail. All patients were "bacteriologically cured" at the time of discharge; however, 11 of the 30 had some degree of impairment of joint function.

Case Reports

Case 1. A 26 year old white male entered St. Louis City Hospital for the first time on November 23, 1949, with the complaint of painful feet, right knee and left ankle of four weeks' duration.

Present Illness: On October 1, 1949, six days following sexual exposure, the patient noted dysuria and a purulent urethral discharge. On October 20 the patient received 300,000 units of penicillin from a local physician. (A urethral smear was not made.) The symptoms decreased in intensity but continued, and four days later he received another 300,000 units of penicillin. The dysuria and urethral discharge subsided. Several days later, the patient noted the onset of a migratory polyarthritis, involving successively the left ankle, right knee and the right first and fifth toes.

The patient was admitted on October 28 to the Midwestern Medical Center, St. Louis, Mo. (U. S. Public Health Service) with the above history. On admission to that institution he did not appear acutely ill; examination revealed swelling, redness and tenderness of the right great toe, right knee, left knee and left ankle. The temperature on admission was 100° F., and the pulse was 80/min. Laboratory data showed a normal blood count; urinalysis was negative; Kahn was negative, and urethral smear was negative for gonococci.

A presumptive diagnosis of gonorrheal arthritis was made, and on October 29 the patient was started on aqueous penicillin, 100,000 units every three hours, and sodium salicylate, 20 gr. four times a day. Aqueous penicillin was continued through November 3, at which time the patient was placed on procaine penicillin with 2 per cent aluminum monostearate, 300,000 units twice a day. This treatment was continued until November 21, when a total dosage of 15,500,000 units had been administered. In addition, fever therapy by means of the Kettering hypertherm was begun on November 1, and the patient received five treatments maintained at 105° F. for five hours each, for a total of 25 hours. He showed definite but not marked symptomatic

improvement on the above therapy. The temperature (except for artificial fever therapy) remained normal after the fifth hospital day. Roentgenograms taken on October 31 showed rather marked destructive joint changes in the right great toe.

Because response to therapy had been incomplete, the patient was transferred to City Hospital for further study on November 23.

Physical examination on admission revealed normal vital signs. Positive findings were limited to the musculoskeletal system. Swelling, redness and tenderness of the right first and fifth toes were extreme. The left ankle was swollen, tender and warm, with limited motion. The right tibial tubercle was exquisitely tender, and the right knee joint contained fluid but was not acutely inflamed.

Laboratory data included a normal complete blood count, negative urinalysis, and negative Kahn test. Gonococcus complement fixation test was negative. Prostatic and urethral massage yielded no secretion. Uric acid, calcium and phosphorus were normal. Sedimentation rate was 36 mm. per hour (Wintrobe—corrected).

Roentgenograms of the involved joints showed a destructive lesion in the interphalangeal joint of the right great toe and erosion of the right tibial tubercle. There was marked periosteal proliferation of the left metatarsal bones. Chest film was negative.

Eight days after admission to City Hospital, the gonococcus complement fixation test was reported positive and remained positive thereafter. The right knee was aspirated and 15 c.c. of turbid yellow fluid were withdrawn. This fluid contained 430 leukocytes/mm.,[3] the majority of which were polymorphonuclear neutrophils. Smears and cultures on this fluid were negative for gonococci; however, the fluid gave a positive gonococcus complement fixation test.

The Frei test was negative. An electrocardiogram was normal. Biopsy of the synovia of the right knee revealed normal synovial membrane and fibrous and adipose tissue. Reëxamination by roentgen-ray failed to reveal any essential change in the radiographic appearance.

On December 22 (one month after admission), the interphalangeal joint of the right great toe was excised and fused. Culture of the bone and joint scrapings failed to reveal any growth. Biopsy revealed chronic granulomatous inflammation compatible with late pyogenic arthritis.

Chemotherapy had been delayed in an effort to procure a bacteriologic diagnosis. Immediately following the above fusion, the patient was started on aureomycin, 0.5 gm. orally every four hours, and streptomycin, 0.5 gm. intramuscularly every six hours. Aureomycin dosage was reduced after five days to 0.25 gm. every three hours. The streptomycin was discontinued after 12 days (total dose, 24 gm.), and the aureomycin was continued for 25 days (total dose, 55 gm.).

The sedimentation rate decreased to 19 mm./hour (corrected) during this period, and later rose to 27 mm. (corrected). The patient showed marked objective and subjective improvement while on aureomycin and streptomycin, and left the hospital (against advice) on January 18, 1950, clinically improved.

He was readmitted to City Hospital on January 25 (one week after signing out of the hospital). In the interval since leaving the hospital he had had intercourse several times with his former wife, and on one occasion drank six bottles of beer and one pint of wine. The involved joints were asymptomatic until one day prior to admission, when swelling and tenderness around the left lateral malleolus and heel developed. The patient insisted that his ex-wife was free of venereal disease, and refused to allow her to be examined.

Physical examination revealed normal vital signs. The patient was barely able to walk because of pain in the left ankle. There was no evidence of genital infection. Swelling and tenderness in the region of the left lateral malleolus and left Achilles tendon were very noticeable. The right great toe was ankylosed and nontender. The

right fifth toe was red, swollen and tender. The right tibial tubercle was slightly tender to very firm pressure.

Laboratory data were normal except for a positive gonococcus complement fixation test and a sedimentation rate of 36 mm./hour (corrected). Roentgen-ray films of the left ankle showed no evidence of bone destruction.

The left ankle was aspirated and culture of the fluid revealed a Neisserian organism which was peroxidase-negative. (Some gonococci do not give peroxidase-positive reaction on primary isolation.[48]) However, the colonies dissolved in 10 per cent sodium hydroxide in the manner reported [49] specific for gonococci. This culture was incubated in 10 per cent carbon dioxide for three days. Previous cultures had been examined and discarded as negative after 48 hours. The organism was very slow growing, and fermentation, sensitivity and thermal death tests could not be obtained.

The patient was again started on aureomycin, 0.5 gm. orally every six hours, and streptomycin, 0.5 gm. intramuscularly every six hours. He remained on this therapy for five days, when he again signed out against advice and the involved joints again showed clinical improvement. Attempts to follow the patient have not been successful.

Discussion: The evidence suggests that this is an instance of gonococcal infection which was unresponsive to intensive penicillin and fever therapy. Improvement followed the administration of streptomycin and aureomycin.

The clinical and laboratory evidence of relapse suggests that the original treatment with streptomycin and aureomycin was inadequate. Although the possibility of reinfection cannot be denied, the time interval seems too short and there was no evidence of genital infection. Response to a second course of aureomycin and streptomycin was prompt and satisfactory.

Case 12. A 35 year year old white male noted urethral discharge three days after exposure. After one week of permanganate irrigations, purulent conjunctivitis developed in one eye and several days later in the other eye. Twelve days after the onset of urethritis, pains developed in the right knee and ankle. The patient then consulted another physician. Smears and cultures of urethral discharge were positive for gonococci. He received aqueous penicillin, 25,000 units intramuscularly every three hours, and sulfadiazine, 1 gm. every four hours. This therapy was continued for four days, and the patient was then transferred to the St. Louis City Hospital because joint symptoms were becoming more severe. Penicillin ointment had been used in the conjunctivae.

Twelve years previously the patient had had gonorrheal urethritis which subsided in three months without complications.

On admission, the temperature was 39.3° C. (102.8° F.); other vital signs were normal. Marked conjunctivitis was present bilaterally, with edema of both lids. There was no iritis or corneal ulceration. There was a slight urethral discharge. The prostate and epididymides were normal. The right ankle and knee were swollen, hot and very tender.

Admission blood count and urinalysis were normal except for a leukocytosis of 12,100. Kahn test was repeatedly negative. Urethral smear was positive for gram-negative diplococci, but urethral as well as conjunctival cultures were negative. Gonococcus complement fixation test was negative 13 days after admission, but thereafter was positive. Roentgenograms of the ankle showed no evidence of bone destruction. Electrocardiogram was normal.

The patient was given aqueous penicillin, 40,000 units intramuscularly every

three hours, and sulfadiazine, 1 gm. every six hours, in addition to penicillin eye drops and boric acid eye irrigations. There was no response to this therapy, and the right wrist became involved. After seven days, artificial fever therapy was added to the above program. Evidence of improvement was prompt after the institution of fever therapy. After two fever treatments, the right knee was aspirated and 70 c.c. of cloudy fluid were withdrawn. Smear and culture of this fluid were negative for gonococci. A total of 24.5 hours of fever over 40° C. (104° F.) was given in a period of 18 days. Penicillin therapy was given for a total of 34 days, the total dose being 10,970,000 units. The patient was asymptomatic and discharged after eleven weeks of hospitalization.

Summary: This patient received 11 days of penicillin therapy prior to the introduction of fever therapy, and during that time the arthritis did not subside and new joints became involved. Response to fever therapy was prompt and complete. A follow-up at the time of writing (three years later) reveals no evidence of arthritis and no residual symptoms.

Case 20. A 28 year old white male was admitted to the St. Louis City Hospital on May 16, 1948, with the complaint of pain and swelling of the left ankle and right knee of three weeks' duration. Three and one-half weeks before admission, the patient had received 800,000 units of penicillin intramuscularly from a local venereal disease clinic because of a purulent urethritis which was positive for gonococci on smear and culture. Two days later the right knee and left ankle became red, hot, swollen and painful. His local physician gave him 300,000 units of penicillin intramuscularly on two occasions. The urethral discharge subsided but joint symptoms persisted, so the patient was admitted to the hospital. For 15 days prior to admission, the patient had been febrile and unable to walk. There was a past history of uncomplicated gonococcal urethritis treated with sulfonamides in 1939.

Examination revealed a man in great discomfort because of joint pain. Temperature was 99.8° F. (37.8° C.) and the pulse was 128 per minute. There was no urethral discharge. The left ankle and right knee were swollen markedly and were red, hot, tender and very painful on the slightest motion. The remainder of the examination was not notable.

Laboratory examinations included a red blood count of 3.2 million/mm.^{3} hemoglobin of 12.5 gm. per cent, white blood count of 14,450/mm.^{3} and a differential count showing a moderate shift to the left. Urinalysis was negative except for the presence of a moderate number of white blood cells. The Kahn test was negative. The gonococcus complement fixation test was strongly positive. The sedimentation rate was 16 mm./ hour (Wintrobe-corrected). Blood culture remained sterile. Prostatic secretions were negative for gonococci by smear and culture on two occasions. Roentgenograms of the involved joints showed no evidence of bone destruction. An electrocardiogram was normal except for sinus tachycardia.

The patient remained febrile and the joints remained acutely inflamed; four days after admission, therapy was instituted. Penicillin was administered intramuscularly every three hours in doses of 60,000 units, and sulfadiazine and sulfamerazine were given, 4 gm. of each initially and 1 gm. every four hours thereafter. The knee was aspirated after two days of therapy; 70 c.c. of fluid were withdrawn, and 20,000 units of penicillin instilled. The white cell count on the fluid was 9,200 per cu. mm., with 90 per cent polymorphonuclear neutrophils. Smear and culture of the fluid were negative for gonococci. After 10 days of therapy there was no evident improvement, and the penicillin dosage was increased to 100,000 units every three hours. After 12 days both sulfonamide drugs were discontinued, a total of 70 gm. of each having been administered. At this time, because of continued fever

and signs of acute arthritis, streptomycin, 0.5 gm. intramuscularly every six hours, and fever therapy in the Kettering hypertherm were added to the continued penicillin therapy. During this time, over an 11 day period the knee was aspirated on three occasions, and decreasing amounts of fluid were obtained. On each occasion, 100,000 units of penicillin were instilled into the joint cavity.

Coincident with the administration of streptomycin and fever therapy, the patient showed the first signs of improvement. The temperature, which had ranged from 100° F. (38° C.) to 101° F. (38.3° C.) daily, subsided after the eleventh day of streptomycin and after 10 hours of fever therapy. The signs and symptoms relevant to the involved joints likewise decreased rapidly. Streptomycin was discontinued after 13 days, a total of 28.5 gm. having been administered. Seven sessions of fever therapy were given over a three-week period, the total hours over 104° F. (40° C.) being 19.25. Penicillin therapy was discontinued four days after the last session of fever and 13 days after the patient became afebrile, the total dose being 28.04 million units. Roentgenograms at this time again showed no joint destruction.

The patient remained asymptomatic without therapy for one week prior to discharge on July 5. During the next five months he was observed in the out-patient department on three occasions. A diagnosis of non-gonococcal prostatitis was made on the basis of clinical and bacteriologic findings. Six months after discharge, the patient had a pain in the right heel; roentgenograms were ordered but he failed to report for them. Follow-up at this time reveals that the patient is perfectly well and free of joint symptoms and signs.

Discussion: After having proved gonococcal urethritis, this patient developed an acute arthritis which failed to respond to penicillin therapy. Improvement coincided with the addition of fever therapy and streptomycin. Since the patient remained free of arthritis for 22 months, a presumptive diagnosis of penicillin-resistant gonococcal arthritis seems justified.

Summary

Thirty cases of gonococcal arthritis have been presented. The clinical picture was characterized by the occurrence of genitourinary gonococcal infection, usually immediately preceding the development of arthritis. The time interval, however, was long in some cases (up to 23 years). The arthritis was characteristically acute in onset, migratory in nature and polyarthritic in distribution. The gonococcus complement fixation test was shown to be a valuable diagnostic aid, especially in those cases in which it became positive during the course of the disease. In only five cases (16.6 per cent) were organisms demonstrated in the joint cavity.

The response to penicillin therapy was in most cases so complete and prompt as to constitute an important diagnostic criterion. In three instances, however, intensive penicillin therapy failed to control the disease, suggesting that an appreciable number of cases may be clinically resistant to penicillin treatment.

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CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS: REPORT OF 37 CASES STUDIED AT THE STATE OF WISCONSIN GENERAL HOSPITAL FROM 1925–1950 *

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Carcinoma of the body and tail of the pancreas is by no means a rarity, yet early diagnosis of this condition has been difficult because the symptom complex has been considered vague and indefinite.

In reviewing the literature since 1939, it was found that several observers have published papers formulating the clinical and pathologic features of this disease. Duff [1] in 1939 reported on 16 cases in which the diagnosis was established at autopsy. He estimates that carcinoma of the body and tail of the pancreas occurs with about one-third the frequency of carcinoma of the head of the pancreas. In his series, abdominal pain was the most common initial symptom, followed by constipation, belching of gas, eructations, swelling of the abdomen and weakness, in that order. These initial symptoms were compared to the initial symptoms in a like number of cases of carcinoma of the head of the pancreas. A marked contrast was noted in that jaundice was an initial symptom in 13 and abdominal pain in only five of 16 cases of carcinoma of the head of the pancreas. The average duration of the illness in Duff's series [1] was slightly over five months. Also, the correct diagnosis was not made in a single instance, in spite of the fact that exploratory laparotomy was performed in four of them.

In studying the pathologic features of carcinoma of the body and tail of the pancreas, Duff [1] stated that there was no difference in histologic features between the head and body and tail types, but explained the deep seated gnawing pain associated with the latter by the fact that the primary tumor, lying in the midportion of the pancreas, is in a position which enables it to erode into the celiac plexus. He also noted that carcinoma of the body and tail metastasized more widely and more massively than that of the head. This, he explained, is due to the anatomic arrangement of adjacent structures, i.e., the head is in contact with the peritoneum in only one relatively small area, at the lower margin of its anterior surface, while much of the body and tail has peritoneal contact. This allows for direct extension, more lymph channel erosion and, consequently, wider metastases. He also noted that liver metastases were more massive in carcinoma of the body and tail than in carcinoma of the head. This, he states, is also explained by the

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anatomy of the region, in that the splenic vein lies in intimate contact with the body and tail, and many short venous channels drain into it.

Levy and Lichtman [2] in 1940 reported on 19 cases of carcinoma of the body and tail of the pancreas, and noted that abdominal pain intensified by the supine position and relieved by sitting and standing was an important feature of the disease. They also noted diabetes mellitus in 15 per cent of their cases, and a remarkable absence of anemia.

Russum and Carp [3] in 1942 reported on eight cases of carcinoma of the body and tail of the pancreas and recognized its relative frequency and the difficulty of diagnosis.

The three papers above represent the only complete summaries of a series of cases of carcinoma of the body and tail of the pancreas observed in searching the literature since 1939. These represent a great advancement since Chauffard [4] first reported three cases in 1908.

Clinical Characteristics

Realizing the difficulties encountered in the diagnosis of carcinoma of the body and tail of the pancreas, the authors undertook this study to discover a definite clinical syndrome which might enable one to establish the early diagnosis. The autopsy and clinical records of all patients with carcinoma of the body and tail of the pancreas admitted to Wisconsin General Hospital between 1924 and 1950 were analyzed. In this manner, 37 cases were found in which the diagnosis was proved at autopsy or laparotomy. Of the 37, 24 were autopsied. Those cases in which the body and tail were involved with extension into the head are not included in order not to confuse a combination of entities.

The average age of these patients on admittance was 58.1 years, the mean, 57 years. As can be seen in table 1, there is a marked predominance of males (31) to six females, or 85 per cent. By "duration" is meant the time from the onset of symptoms until death or discharge from the hospital. The duration of the disease is not entirely accurate because only 24 cases were followed until death; the other 14 were discharged to their homes and the exact time of death is not known. With this inaccuracy in mind the average duration is 6.3 months for the total 37 cases, and 9.1 months for those followed to necropsy.

The most common chief complaint of these patients on admission was "pain in the stomach" (18 cases, or 48 per cent). Back pain was the chief complaint in six cases. At autopsy, cases 2, 13, 14, 15, 21, 22, 26 and 34 revealed carcinoma of the tail, the remaining cases having involvement of the body alone or body and tail combined. No significant difference in symptoms was noted between tail and body involvement.

The heading "diagnosis on admission" warrants further explanation. The Wisconsin General Hospital serves as a diagnostic and treatment center for doctors throughout the State of Wisconsin, and "diagnosis on admis-

TABLE I

Case	Age	Sex	Duration	Chief Complaint	Diagnosis on Admission	Final Clinical Diagnosis before Laparotomy or Autopsy
1	38	M	* 8 mos.	Priapism	Myelogenous leukemia	Cancer of pancreas leukemia
2	44	M	* 2 mos.	Abdominal pain	Brain tumor	Cancer of body of pancreas and liver cirrhosis
3	69	M	*12 mos.	Back pain	Hemorrhoids with abdominal complications	Rectal cancer or hypernephroma with metastasis
4	67	M	* 3 mos.	Pain in abdomen	Gastric cancer or peptic ulcer	Cancer of the stomach
5	72	M	* 3 mos.	Constipation	Cancer of bowel	Cancer of the rectum
6	57	M	* 6 mos.	Pain in right shoulder and back and weight loss	?	Hypernephroma
7	53	M	* 2 mos.	Pain in epigastrium, fever and chills	Malignancy	Cancer of body of the pancreas or stomach
8	57	M	* 5 mos.	Pain in right shoulder, left lower quadrant, epigastrium	?	Cancer of head of pancreas or stomach
9	53	M	*24 mos.	Pain in left side	Tumor? Herniated intervertebral disk. Prostatic hypertrophy	Herniated disk (intervertebral), osteoarthritis of spine, psychoneurotic
10	72	M	*30 mos.	Cannot pass urine	Pernicious anemia	Nutritional deficiency
11	56	M	* 3 mos.	Ache in back	Kidney tumor	Cancer of sigmoid
12	67	M	* 3 mos.	Pain in chest and stomach	Cancer	Cancer of pancreas suspected, also cancer of sigmoid
13	46	M	* 7 mos.	Back pain over kidney and lower chest	Kidney tumor	Cancer of stomach
14	29	F	*12 mos.	Headache	Ovarian insufficiency	Metastatic cancer from ovary
15	69	M	* 6 mos.	Pain in abdomen	G. I. malignancy	Cancer of lower bowel
16	47	M	* 5 mos.	Abdominal pain	?	Deferred
17	60	M	* 1 mo.	Dull epigastric pain	G. I. malignancy	Cancer of G. I. tract
18	62	M	* 2 mos.	Fever and pain	?	Hepatitis, liver cancer, primary unknown
19	62	M	*60 mos.	Swelling in abdomen	Malignancy?	Cancer of colon
20	74	M	*2½ mos.	Pain in abdomen	?	Cancer of stomach
21	55	M	* 5 mos.	Swollen throat	Osteosarcoma of left temporal region	Hypernephroma
22	69	M	* 3 mos.	Pain in stomach	Abdominal tumor	Bowel neoplasm, lymphosarcoma
23	53	M	* 4 mos.	Weakness	?	Cancer of head of pancreas, cancer of gall-bladder
24	57	M	*12 mos.	Epigastric pain	Pancreatitis	Pancreatic tumor
25	62	M	15 mos.	Pain in abdomen	?	Peptic ulcer, cancer of small bowel
26	36	M	8 mos.	Feeling run down	Cancer of liver	Cancer of liver, T. B., brucellosis, lymphoma, cirrhosis
27	54	M	4 mos.	Something wrong with stomach	Acute gastric condition	Cancer of pancreas
28	43	M	13 mos.	Pain in left side of stomach	?	Cancer of colon
29	69	F	4 mos.	Pain in stomach	Visceral cancer	Cancer of stomach or cancer of pancreas body
30	75	F	2 mos.	Abdomen bloated	?	Cancer of colon or cancer of pelvic organ
31	57	M	1½ mos.	Pain in abdomen and back	Cancer	Adhesions, postoperative
32	52	F	6 mos.	Distress on eating	?	Cancer of pelvic organs
33	56	F	4 mos.	Loss of appetite, nausea and vomiting	?	Cancer of stomach
34	41	M	3 mos.	Pain in epigastrium	?	Peptic ulcer
35	66	M	9 mos.	Pain in stomach	Gastric ulcer	Cancer of ascending colon
36	67	M	4 mos.	Weakness	Cancer	?
37	73	M	3 mos.	Constipation, blood in urine	Cancer	Kidney tumor

* Autopsied cases.

sion" pertains to the diagnosis made by the referring doctor. As is apparent, the diagnosis of carcinoma of the body and tail of the pancreas was not made in a single case, although "carcinoma" or "carcinoma of the gastrointestinal tract" is frequent. Pancreatitis was suspected in one case, and no diagnosis made in 12.

By "final diagnosis before laparotomy or autopsy" is meant the diagnosis made by the staff of Wisconsin General Hospital after all laboratory and x-ray studies were completed. Carcinoma of the body and tail of the pancreas was seriously considered by some member of the house staff in

only seven cases, or 18 per cent. Three patients were diagnosed as psychoneurotic.

It is of interest that two cases had laparotomies during the course of their disease before admission without discovery of the tumor.

In table 2 the clinical signs and symptoms are tabulated. As can be seen, weight loss (97 per cent), pain (97 per cent), anemia (81 per cent) and constipation (51 per cent) make up the common findings. The frequency of the anemia does not coincide with Levy and Litchman's [2] series, in which anemia was a rarity. This anemia, in the majority of cases, was hypochromic in type and was found commonly on admission and does not represent a terminal finding. The pain will be described in greater detail later. A change in bowel habit was manifest by constipation in 51 per cent of the cases; although diarrhea was noted in 19 per cent, melena was present in only 8 per cent. Ascites was present in 12 cases, or 32 per cent, usually noted late in the disease. In all 12 cases with ascites, liver metastases combined with peritoneal implants or portal vein thromboses were found at necropsy or laparotomy. This finding agrees with Duff,[1] and consequently, if ascites is discovered in a patient with carcinoma of the body and tail of the pancreas, one may, for all practical purposes, conclude that liver or peritoneal metastases have occurred. Also, in three cases fever and sweats were symptoms. The cause of this is not known, but it may be attributed to liver metastases, since in all three cases liver metastases were found at necropsy.

TABLE II

No.	Signs and Symptoms	No. of Cases	%
1	Pain (any type)	36	97
2	Weight loss	36	97
3	Anemia	30	81
4	Constipation	19	51
5	Nausea and vomiting	17	46
6	Anorexia	15	41
7	Epigastric tenderness	14	38
8	Ascites	12	32
9	Weakness	12	32
10	Venous thromboses	11	30
11	Jaundice	8	22
12	Gas	8	22
13	Mass palpable in epigastrium	8	22
14	Diarrhea	7	19
15	Mass palpable in rectum	5	14
16	Fever	3	8
17	Sweats	3	8
18	Melena	3	8
19	Early satiety	3	8
20	Virchow's node	2	5
21	Nodule in abdominal wall	2	5
22	Chills	1	3
23	Hematemesis	1	3
24	Hematuria	1	3
25	G.I. series negative	22	60
26	Intestinal obstruction	4	11
27	G.I. series show mass displacing stomach posteriorly	3	8
28	Elevated blood sugar	3	8

A positive physical finding noted in 14 cases (38 per cent) was epigastric tenderness. A complete gastrointestinal x-ray study was done in 29 cases. In 22 the x-rays were negative, in two intestinal obstruction in the transverse colon was noted, in two, duodenal ulceration, and in three the stomach was displaced posteriorly by an extrinsic mass. In two cases which revealed a negative gastrointestinal series, transverse colon obstruction was noted at autopsy.

There was evidence of diabetes mellitus in only three cases, and in only one (case 10) was there evidence of pancreatic dysfunction, manifested by elevated fat and undigested protein in the stools. Serum amylase was measured in only five cases. In two cases it was below normal, in one it was at the lower limits of normal, and in two it was normal. It is unfortunate that more serum amylase levels were not obtained, as well as urine diastase excretions.

TABLE III

Evaluation of Pain

Classification	No.	%
1. Pain of any type	36	97
2. Localization:		
A. Epigastric	32	86
1. No radiation	15	43
2. Radiation to back	11	30
a. Via left side	2	5
b. Via right side	0	0
c. Straight through	6	17
3. Left lower quadrant	2	5
4. Generalized abdominal	2	5
B. Back pain only	2	5
C. Right shoulder	1	3
D. Precordial	1	3
3. Aggravated by supine position, relieved by sitting up	15	43
4. Aggravated by motion	1	3
5. Aggravated by food	12	33
6. Relieved by food	3	8

In table 3 is found the evaluation of pain which occurred in all but one of the patients. The most common site of pain was epigastric (86 per cent), with radiation to the back in 30 per cent. The direction of radiation was indefinite in most patients. An important characteristic of the pain was its relation to position: it was relieved by sitting up and aggravated by lying down in almost half of the cases (43 per cent). There was also a relationship to food intake, 33 per cent being aggravated by food intake. The epigastric pain showed no definite relationship with erosion of the stomach or duodenum, since only two cases revealed duodenal ulceration at autopsy.

As early as 1866 Trousseau [5] observed the relationship of venous thrombosis and malignant tumors of epithelial origin. In 1938 Sproul [6] first pointed out the frequent association of venous thrombi and carcinoma of the body and tail of the pancreas. As she stated, the thrombosis of a single vessel is not so significant as multiple thrombi, since a single vessel

might well be thrombosed without relationship to a tumor in the body. Sproul studied the incidence of thrombosis in carcinoma of various organs and found that carcinoma of the body or tail of the pancreas, lung and stomach were associated with the greatest number of venous thromboses. In her series, 56.2 per cent of the cases of carcinoma of the body and tail of the pancreas had single venous thrombosis and 31.3 per cent multiple thrombi. Lung carcinoma showed an incidence of multiple thrombi of 2.5 per cent, stomach carcinoma of 1.3 per cent. The reason for this association is not known. Sproul proved that it was not due to invasion of the vein wall by tumor cells. She postulates that it may be due to an interference with the blood clotting mechanism, i.e., the tumor cells increase the trypsin content of the circulating blood. Trypsin is believed to hasten clotting by changing the protein molecules and altering the surface forces that cause clotting. Another theory is that the tumor cells increase the lipase concentration in the duodenum, thus hastening the digestion of fats and vitamin K absorption and followed by greater prothrombin production and shortened blood coagulation time.

TABLE IV

Incidence of Venous Thrombi

Classification	No.	%
1. One or more venous thrombi	11	30
2. Multiple venous thrombi	8	22
3. Vein involved		
A. Iliac vein	5	14
B. Femoral vein	4	11
C. Portal vein	3	8
D. Splenic vein	3	8
E. Inferior vena cava	3	8
F. Pulmonary vein	2	5
G. Antecubital veins	1	3
H. Superior mesenteric	1	3
I. Vein of foot	1	3
J. Corpus cavernosum	1	3
4. Evidence of venous thrombi clinically	7	19
5. Evidence of venous thrombi at autopsy	10	27

Kenny [7] in 1943 also pointed out the association of venous thrombi with carcinoma of the body and tail of the pancreas. He reviewed 30 cases of carcinoma of the head of the pancreas and 21 of the body and tail. The cases of carcinoma of the head revealed no case of multiple venous thrombi, while those of the body and tail showed an incidence of multiple venous thrombi in 33 per cent and single venous thrombi in 47.6 per cent. He suggested that this high percentage of thromboses was due to secretion of an abnormal substance by the tumor cells, or to an undue secretion of normal substance concerned in blood clotting. His assumption was supported by the fact that in every case showing multiple venous thrombi the tumor was of the mucinous type, and no tumor without mucin showed the phenomenon. In view of the great difficulty in diagnosis of this condition, he urged that

every patient suspected of having carcinoma of the body and tail of the pancreas be thoroughly examined for evidence of venous thrombosis and have the blood clotting mechanism studied thoroughly.

Table 4 shows the incidence of venous thrombi in the 37 cases studied at Wisconsin General Hospital. As can be seen, the percentage of venous thrombi is 30 and of multiple venous thrombi 22. This is somewhat lower than the percentage reported by Sproul [6] and Kenny.[7] In seven of the 11 cases the thrombosis was noted clinically. With such a paucity of signs to aid in diagnosing carcinoma of the body and tail of the pancreas, one must search closely for venous thrombosis to make an early diagnosis. Kenny [7] believes venous thrombosis is an early sign, and this was found to be true in this series. Also the percentage of thrombi might have been greater if a more careful search had been made before and at autopsy. In the 24 cases autopsied in this series there was no dissection of the extremities, and no special effort was made to discover venous thrombi. The iliac and femoral veins were most frequently involved with thrombosis.

Summary

Thirty-seven cases of carcinoma of the body and tail of the pancreas were reviewed in order to formulate a definite combination of signs and symptoms which may permit early diagnosis.

A marked predominance of males (84 per cent) was found. The average age was 58.1 years; duration of illness, nine and one-tenth months. The correct diagnosis was made in only seven cases before laparotomy or autopsy, the common incorrect diagnosis being carcinoma of the colon.

The most common symptoms were abdominal pain, weight loss, anemia, nausea, vomiting and constipation.

Two findings which were unique, and which appeared with significant frequency in this disease, were venous thrombi and abdominal pain related to position. Multiple venous thrombi were noted in 22 per cent, the common veins affected being the femoral and iliacs. Abdominal pain aggravated by the supine position and relieved by erect position was noted in 43 per cent.

Ascites implies liver or peritoneal metastasis or portal vein thrombosis. Barium studies of the gastrointestinal tract were negative in the majority of the cases.

Conclusion

The difficulty of early diagnosis is apparent, and early search for venous thrombi and thorough blood studies in regard to amylase, prothrombin and clotting factors are urged.

The combination of weight loss, anemia, constipation, venous thrombosis and otherwise unexplained abdominal pain aggravated by the supine position should suggest immediately the possibility of carcinoma of the body of the pancreas.

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PEPTIC ULCER: MEDICAL CURE BY EFFICIENT GASTRIC ACID NEUTRALIZATION *

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Introduction

In two communications [1, 2] evaluating a number of commonly used antacids utilizing a continuous pH recorder in vivo and in vitro, Rossett and Flexner concluded that magnesium oxide, peroxide, hydroxide and carbonate, as well as calcium carbonate, when combined with an amphoteric substance such as milk or aluminum hydroxide gel, were efficiently buffered in their alkaline range preventing rebound and produced long-acting antacids. A promise of clinical evaluation of such antacids made at that time could not be effectively fulfilled because of World War II service and until the senior author had the opportunity of supervising a large gastrointestinal section (106 beds) such as is present at Kennedy Hospital. This paper attempts to fulfill that promise.

The title of this paper deliberately paraphrases the title of Bertram W. Sippy's paper published in 1915.[3] We believe our work is merely an extension of his, permitted by time and the progress of other sciences.

The present generally accepted concept of the pathogenesis of peptic ulceration is summarized below.

The oral passive receptivist (to use the psychoanalyst's shorthand for the peptic ulcer personality), frustrated in his need for love, esteem and care, cortically produces vagal stimulation. Electroencephalograms have shown alpha wave preponderance in peptic ulcer patients, possibly associated with this stimulation.[4, 5] Vagal stimulation causes gastric hypertonicity and hypersecretion activities of the stomach which, when sufficiently intense and prolonged, may lead to ulcer formation. Psychiatric therapy (cortical level) has proved effective, but relatively few reported cases are available.[6, 7, 8] Its cost remains prohibitive for the great majority of peptic ulcer patients. Dragstedt [9, 10] again attacked the problem at the vagal level. The prompt relief of ulcer distress and infrequent recurrence produced by vagotomy are being weighed against frequent instances of gastric atony and retention, foul smelling eructations, diarrhea, dysphagia, curious abdominal colicky pain and weakness.[11] In addition, the long-term sequelae of deprivation

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of parasympathetic innervation of the biliary tract, pancreas, small intestine and kidneys are yet to be determined.

Sippy's work at the gastric level was monumental.[3] He summarized 12 years of experience in antacid therapy with this statement: "The striking results to be obtained by applying the principle of accurately protecting the ulcer from gastric juice corrosion would seem to be the best evidence yet produced in substantiation of the old corrosion theory of peptic or digestive ulcer." Thirty-five years have left the statement as valid as when it was made. Sippy's plan of management included three to four weeks of bed rest, and hourly feedings from 7 a.m. to 7 p.m. Powder alkalis were given every half-hour after the last feeding until 10 p.m. Night secretions, if very acid, were drained.

The frequent occurrence of alkalosis,[12] the probably unjustified fear of renal calculi,[13] patient intolerance to being disturbed every half-hour, and the additional time and care demanded of dietitians, nurses and physicians discouraged the full realization of Sippy's "principle" in the past. Newer antacids and an increased knowledge of the action of old ones permit this achievement with little fear of disturbance of acid base balance and with great amelioration of patient distaste and demands on staff time and care.

Rossett and Flexner's [1, 2] in vitro experiments used 30 c.c. of N/10 HCl in 70 c.c. of distilled water (pH 1.4) to simulate the fasting contents of the hyperchlorhydric stomach. Tenth-normal HCl was added at the rate of 120 c.c. hourly to simulate the secretion of the hyperchlorhydric stomach. Their in vivo experiments with a glass electrode located in the bottom of a stomach tube, or with gastric contents led by tube to a commercial continuous recording pH meter, gave results strikingly similar to the in vitro experiments. They concluded that the latter method was an adequate procedure for an analysis of the efficacy of antacids. Figure 1 illustrates the effectiveness of antacid combinations described in the first paragraph of this paper, contrasted with an antacid such as calcium carbonate alone using the in vitro titration method.

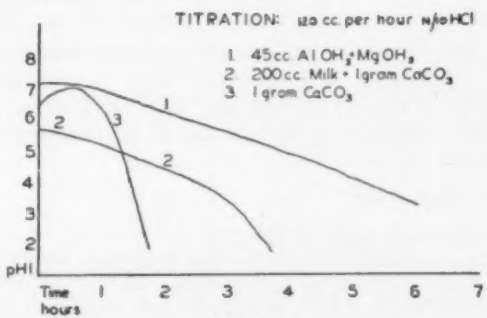

FIG. 1.

It shows superimposed titration curves of 1.0 gm. of calcium carbonate, 200 c.c. of sweet milk with 1.0 gm. of calcium carbonate, and 45 c.c. of a mixture of aluminum hydroxide gel (5.5 per cent), four parts by volume, and milk of magnesia (U.S.P.), one part by volume. Calcium carbonate in milk retains its individual long-acting antacid property and is buffered in the alkaline range, in the given quantities. The mixture of aluminum hydroxide gel with milk of magnesia proves to be the longest acting antacid of those considered. Forty-five cubic centimeters of the mixture contain only 9 c.c. of U.S.P. milk of magnesia, which are not less than 0.63 nor more than 0.76 gm. of magnesium hydroxide.

Method

A. Antacids: Calcium carbonate with magnesium oxide in milk, when protein from food or blood was in the stomach, and a mixture of aluminum hydroxide gel and milk of magnesia, when the stomach was empty or contained little protein, were the antacids selected for use in the treatment schedules which are presented in outline.

B. Dietary: The ulcer diet adhered to the generally accepted principles listed below:

1. Omit gastric secretagogues. This excludes alcohol; caffeine-containing beverages such as coffee, tea, Coca-Cola, Spur, Rock-Cola, etc.; condiments; meat extractives; seasoning, and citrus fruits.
2. Omit coarse foods which might traumatize the ulcer or the gastric or duodenal mucosa. This excludes vegetables with coarse cellulose, fibrous meats or hard fried foods, etc.
3. Omit very hot and very cold foods.
4. Avoid overdistention to avoid hyperperistalsis and hypersecretion.
5. Provide all of the essential food elements which are necessary for maximal nutrition.
6. Furnish 100 to 150 gm. of protein daily, primarily for its neutralizing capacity but also for its ability to satisfy nutritional protein needs and possible deficiency present as the result of previous dietary limitation.

The citrus fruits were omitted because of a possible secretagogue effect. Ascorbic acid supplements of 50 mg. daily were substituted. When obstruction or bleeding was not present, beef steak, lamb chops, lobsters, etc., were fed without hesitation on the first day of hospitalization.

C. Treatment Schedules:

1. *Uncomplicated Peptic Ulcer:*

Bed-rest.

Ulcer diet with ascorbic acid, .05 gm. daily.

Mixture of aluminum hydroxide gel and milk of magnesia, 45 c.c. between meals, 8 p.m., bedtime, and every two hours through 6 a.m.

Tincture of belladonna, 1.5 c.c. every six hours increased by 0.5 c.c. steps cautiously as required.

Neutralization was determined by gastric emptying at 8 a.m. before feeding. This was done by placing the patient in the prone Trendelenburg position after passage of a 36F Ewald stomach tube, as when patients are emptied for gastroscopy.

Unless this method is used it is a physical impossibility to check neutralization on any large service. With this method, patient coöperation is readily obtained. Successful passage of the large stomach tube and gastric drainage were achieved without exception, a situation not reproducible with a small soft stomach tube. It is illustrated in figure 2.

Empty stomach at 8 a.m. to verify neutralization. Increase antacids to 150 c.c. every two hours as required to secure neutralization. If rapid gastric emptying prevents this, 30 to 45 c.c. every hour usually succeeds.

FIG. 2.

Bed-rest for five days after all pain ceases (usually 10 days total), or until niche when demonstrable disappears radiographically.

Ambulate patient and continue same diet and antacid medication another week.

Substitute milk for the antacid mixture the last three days of hospitalization and discontinue night feedings and tincture of belladonna. If patient is obese, use only skimmed milk.

2. *Bleeding Peptic Ulcer:*

Bed-rest.

Use barbiturates for sedation. Oral seconal, 0.1 every six hours, or sodium amytal, intramuscularly as required when vomiting is present.

Modified Meulengracht regimen of feeding soft, bland foods every two hours during day. Achieve partial neutralization by adding 0.9 gm. calcium carbonate with 0.1 gm. of magnesium oxide to 200 c.c. of milk in feedings every two hours through the night.

Vary the quantity of magnesium oxide as necessary to control bowel movement.

Oral tincture of belladonna, 1.5 c.c., or atropine, 1 mg. every six hours if vomiting is present.

Gastrointestinal series within first four days.

Change to mixture of aluminum hydroxide gel milk of magnesia at bedtime and every two hours through night when bleeding has ceased for about five days.

Following this, place patient on the uncomplicated ulcer diet and ambulate.

3. *Peptic Ulcer with Obstruction:*

Eight a.m. and 10 p.m. stomach drainage, using 36F stomach tube with patient in prone Trendelenburg position.

Meal or milk and alkali immediately after drainage.

Liquid diet of skimmed boiled milk hourly, the quantity at one feeding being equal to the quantity the patient was able to pass through his obstruction divided by the number of daily feedings. If quantity is 150 c.c. or less, add $CaCo_3$, 0.45 gm., MgO, 0.05 gm. to each feeding. Avoid alkalosis by decreasing these antacids if necessary.

Start feedings at 8 a.m. and end at 10 p.m.

Tincture of belladonna, 1.5 c.c. every six hours.

Achieve neutralization at night by giving 45 c.c. or more every two hours of the mixture of aluminum hydroxide gel and milk of magnesia, as determined by acidity of 8 a.m. specimen.

Restore electrolyte balance when indicated by parenteral administration of saline and, if nutrition is poor, dextrose and amino acids.

Satisfy vitamin requirements by adding them to the feedings or the parenteral fluids.

When 3,000 c.c. of the milk are emptied normally, add gradually soft foods such as very soft boiled eggs, Cream of Wheat, etc., until patient can tolerate full ulcer diet.

Results

These antacids and the regimens outlined have been used exclusively in patients hospitalized in the Gastroenterology Sections of Ashburn General Hospital, McKinney, Texas, from December, 1943, to November, 1945; of Brooke General Hospital, Fort Sam Houston, Texas, from December, 1945, to April, 1946; and of the Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee, from September, 1946, to the present (October 1, 1950).

In no single instance in 182 consecutive uncomplicated peptic ulcer patients in Army General Hospitals, and 1,106 consecutive patients in Kennedy Veterans Administration Hospital, has there been a failure to stop ulcer pain completely and to produce healing. There has not been an instance in this group of hemorrhage, obstruction or perforation while under treatment.

Persistence of pain possibly attributable to peptic ulceration was noted in only two patients beyond 14 days of therapy. In both, radiographic evidence of complete healing was obtained. One patient at Ashburn General Hospital in 1944 had one year of continuous pain. Exploratory operation revealed a healed ulcer. On awakening from operation the patient noted complete relief of pain, although no procedure other than laparotomy had been done. The second patient had two niches demonstrated radiographically, as well as prompt healing in two weeks of therapy. In spite

of this, epigastric pain radiating to the right nipple had persisted, although ameliorated. Subtotal resection and bilateral vagotomy, done March 26, 1948, revealed two healed and epithelialized ulcers. Postoperatively, further pain amelioration was noted, and the pain radiation had dropped to the right subcostal margin. Most strikingly, recurrent headache had disappeared. A two-year follow-up revealed that constant pain had been present since operation, although patient is gastroscopically and radiographically negative. In both these patients we believe the residual pain to be psychogenic in origin. Operation confirmed our belief that no uncomplicated ulcer was intractable to therapy.

There have been two deaths in 168 episodes of severe gastrointestinal bleeding. Autopsy or radiographic confirmation of ulceration was not secured in either fatality. All of those who survived had radiographic confirmation of niche, niche and constant deformity, or constant deformity alone. An additional 23 probable bleeding ulcer patients are not included, but could only alter the figures favorably, for all survived. A more detailed report of our management and results in the first 150 patients with this complication has been published.[14]

Statistical data derived from these patients suggest that we were dealing with a not unusual sampling, except that only four patients were females, and the age group, 40 to 48 (112 patients), was small, consistent with this usual divergence in World War I and II veteran populations. The mean patient age was 38.1 years, with a range of 18 to 82 years. An ulcer history of over four years' duration was present in 1,024 patients. There were 237 colored patients. The only statistically significant fact derived by comparing this group with the white group was that their pain localization was more likely to be bizarre. Eighty-four gastric ulcers were found and treated (5.3 per cent). There were 1,493 duodenal, six jejunal, one gastric and duodenal, and one duodenal and jejunal ulcers. There were 314 readmissions. Sleep cycle disturbance, seen in over 95 per cent of the patients without organic disease, was found rather infrequently in this group. Tossing for longer than a half-hour before sleep was noted in only 96 patients, and fatigue on arising in only 84. The combination appeared in only 67 patients (4.2 per cent). Night pain appeared in 41 per cent of the cases, most frequently before 2 a.m., and usually at the same time for any patient. It appeared after 3 a.m. in only 23 and after 4 a.m. in only eight of 656 patients with this symptom (3.5 and 1.2 per cent, respectively). With two exceptions, all had some pain-free interval between attacks. Without exception, ulcer pain was amenable to therapy. Table 1 illustrates the time required to achieve complete freedom from ulcer pain. Complete disappearance of pain had to be gauged by response to the question, "Do you have any pain at all?" Patients grateful for the amelioration of agonizing pain will state that they are fine, yet further questioning elicits the presence of mild pain. The time necessary for pain to disappear com-

pletely was significantly decreased by starting patients on 60 c.c. of the aluminum hydroxide milk of magnesia mixture every two hours through the night, with 1.5 c.c. of tincture of belladonna every six hours, followed by decrease or increase as results from morning drainages were obtained. This is now our method of determining antacid requirements. It permits rapid achievement of "free achlorhydria." "Free achlorhydria" was that evidenced by a negative reaction to Topfer's reagent (pH 3–4.5), essentially absence of free HCl. Radiographic demonstration of the actual ulcer or niche was successfully accomplished in 685 patients of 1,585 in this series, or 43.2 per cent. In only 30 cases was a diagnosis of ulcer made on clinical findings and history without being able to demonstrate deformity or niche formation or both (less than 2 per cent). Roentgen-ray healing time could be determined with accuracy only in the gastric ulcer and in the readily visualized duodenal niches, aided by compression and a filming fluoroscope.

TABLE I

Time Required to Become Pain-free

Days	Duodenal	Gastric
1	300	22
2	292	17
3	305	10
4	93	6
5	60	3
6	37	0
7	54	0
8	18	0
9	11	0
10	15	0
11	2	0
12	2	0
13	3	0

The remainder were not accurately determinable from records, but all were under two weeks.

All demonstrable craters healed within six weeks. Radiographic follow-up was usually done weekly. These results appear better than the only other reported large series, by Cummins, Grossman and Ivy,[15] who used a strict Sippy diet, atropine in smaller doses and sedation. Their average healing time for 63 duodenal craters was 40 days, with a range of 13 to 230 days, which contrast with 506 duodenal craters which could be roentgen-rayed weekly in this series, with an average healing time of 2.16 weeks, or 15 days, with a range of one to six weeks. Their average healing time for six gastric craters was 42 days, with a range of 18 to 68 days, which contrasts with 36 gastric craters in this series with an average healing time of 2.41 weeks, or 16.9 days, with a range of one to five weeks. (See table 2.) The group of bleeding peptic ulcers was weighted in the younger age brackets, but severity is comparable to other reports. Transfusions were used freely at a rate of 125 to 250 c.c. per hour. In one patient, 6,000 c.c.

were given in 36 hours with recovery. One patient who recovered received 9,500 c.c. of blood over an eight day period, and we would not hesitate to give more if necessary. Only three patients with hemorrhage were subjected to emergency surgical intervention; all survived. There were 129 cases with obstruction. All but three were opened sufficiently to achieve positive nitrogen balance and weight gain. They and 69 other obstructors had surgical correction.

Tincture of belladonna has been raised to as much as 4 c.c. every six hours in selected young patients. Subjective complaints of blurred vision and dry mouth were met with reassurance. A toxic psychosis was encountered in three (aged 28, 55, and 55 years) of 694 patients given tincture of belladonna. The dose in each was only 1.5 c.c. every six hours. Satisfactory response to withdrawal occurred in one and one-half days. Mild dysuria was encountered 11 times, principally in the older age group.

TABLE II

Time Required for Crater Healing

Weeks	Duodenal	Gastric
1	84	2
2	294	19
3	97	13
4	24	2
5	3	0
6	4	0
	506	36

No other toxic effects severe enough to force discontinuance of the tincture were encountered. Tincture of belladonna was limited to 1.5 c.c. every six hours in patients over 45 years of age for fear of precipitating glaucoma, although this complication fortunately as yet has not been encountered.

DISCUSSION

Milk of magnesia, rather than magnesium oxide, carbonate or peroxide, was used with the aluminum hydroxide because it is more conveniently secured and measured and is already in good suspension. In the proportions used (four parts of aluminum hydroxide to one part of milk of magnesia by volume), few patients noted change in bowel habit. In some instances the content of milk of magnesia had to be changed to provide a single daily bowel movement. The combination of milk of magnesia with aluminum hydroxide gel provides the longest acting antacid. It cannot be used when protein is present in the stomach, however, because of the formation of a coagulum which is constipating, removes buffer and may produce obstruction.[16] Rarely was intolerance to the mixture encountered. In these patients, the calcium carbonate plus magnesium oxide powder in milk was used.

The calcium carbonate and magnesium oxide in milk provide a long-acting antacid without rebound which is effective when protein is present in the stomach. Magnesium oxide was added to the calcium carbonate because it is five times as effective by weight as an antacid and overcomes the constipating effect of the latter. Both are so-called nonsystemic antacids, although not absolute, and do not permanently remove the acidifying effect of the gastric contents. This permits the latter to be available for neutralization of the alkaline digestive juices present in the small intestine. Clinical alkalosis has been encountered only once in the 10 year period in which these antacids have been used (in a decompensated and obstructed cardiac patient).

At some time during treatment, all patients were required to attend classes in ulcer diet and regimen given by the ward physician and dietitians. Of tremendous assistance was the attendance of the cook of the patient's household, for obvious reasons.

In uncomplicated peptic ulcer, the ulcer diet was started on admission. The patient was therefore on the diet we expected him to follow for the rest of his life, surgeon, radiotherapist or psychiatrist not intervening. His education in living with his disease began, at least by precept, on his first hospital day. The effect on nutritional status and psyche was most salutary. The rate of ulcer healing was astonishing.

The "bleeder" regimen was so greatly modified that it is perhaps a misnomer to call it a Meulengracht diet.[17] The name has been retained to indicate our admiration for a plan that permits acid neutralization and adequate nutrition at the earliest moment (when the patient has ceased vomiting). It differs in these ways:

1. Feedings were ground or pureed initially, bland, and were given every two hours instead of every three.
2. Feedings were continued around the clock.
3. Tincture of belladonna or atropine and antacids were used regularly, not only when pain was present.
4. Blood transfusion was used freely.

When vomiting was present it was treated by absolute abstinence from oral intake. Cracked ice serves no function in these patients, the attitude toward it being that "cracked ice equals oral fluids in the quantity given." The patient with a bleeding ulcer was given the poorer antacid mixture of milk, calcium carbonate and magnesium oxide, instead of aluminum hydroxide gel milk of magnesia mixture, because of the presence of blood (an excellent amphoteric protein) in the stomach. The criteria for inclusion in this group were hospital-verified gross hematemesis with grossly tarry stools concomitantly or appearing within a few days, and grossly tarry

stools alone with roentgen-ray confirmation of peptic ulceration in both groups.

Sedation and antispasmodics were specifically omitted until July, 1948 (except a barbiturate during the first few days of active bleeding, as required), to permit better evaluation of antacid therapy. Since that time, patients have had atropinization and complete tobacco abstinence added to their regimen. The atropinization appears to decrease the amount of aluminum hydroxide gel milk of magnesia mixture every two hours needed to achieve "free achlorhydria" by 15 to 30 c.c. We have used Banthine® in 25 patients not included in this study who initially had "free achlorhydria" produced by our usual antacids and tincture of belladonna. Banthine in 50 to 100 mg. doses appears capable of substituting for the tincture of belladonna used in our ulcer treatment schedules.

It is probable that some of our patients were not completely neutralized during the early sleeping hours, in spite of verification of "free achlorhydria" by tube at 8 a.m. Secretion during the forenight is frequently greater and of higher acidity than from 4 to 8 a.m.[18] Eight patients had to be given 30 c.c. of the mixture of aluminum hydroxide gel and milk of magnesia every hour with 1.5 c.c. of tincture to secure "free achlorhydria," because 150 c.c. of the mixture alone every two hours failed to produce "free achlorhydria," apparently due to rapid emptying of the antacid. One young "two time perforator" required 90 c.c. of the mixture every hour and 3 c.c. of the tincture every six hours to produce "free achlorhydria." Neutralization during the day was achieved by feeding high protein meals, with 45 c.c. of the mixture of aluminum hydroxide gel and milk of magnesia between meals and two hours after the last meal. The average high protein ulcer meal produces "free achlorhydria" for about two hours.

The obstructed peptic ulcer patient represents an exact problem in nutrition and therapeutics. Nutrition was maintained by furnishing all requirements by vein and by mouth. Boiled skimmed milk was used to provide a fine curd and obviate the delay in gastric emptying caused by fat. As the obstruction diminished under the regimen described, the parenteral administration diminished accordingly. Tincture of belladonna was initiated cautiously in this group for fear of delayed emptying as the result of decreased gastric motility. The benefits of readier achievement of achlorhydria (most difficult in this group) appeared definitely to outweigh this possibility, as determined empirically by decrease in retention. Only three of 129 obstructed patients were unable to advance to the full uncomplicated ulcer diet and regimen. They and 66 other obstructed patients, believed very probable candidates for recurrence, who went to surgery, were in the best possible nutritional status for operation with a decompressed and compensated stomach.

The dietitian had only two diets to concern her, the ulcer and the bleeding ulcer diet. She did, however, have to teach classes in ulcer dietary.

Conclusions

1. Aluminum hydroxide gel with one-fifth (by volume) of milk of magnesia is a long-acting, nonconstipating antacid in the stomach containing little or no protein.

2. Calcium carbonate with one-tenth (by weight) of magnesium oxide in milk is a long-acting antacid, buffered in the alkaline range, without rebound, not productive of constipation or diarrhea in the stomach containing protein.

3. These antacids, in combination with described high protein feedings, used so that Bertram W. Sippy's principle of accurately protecting the ulcer from gastric juice corrosion was achieved, have produced pain cessation and ulcer healing in 1,288 hospitalized consecutive uncomplicated ulcer patients without exception or occurrence of a single episode of obstruction, perforation or bleeding while under therapy. Two deaths occurred in 168 consecutive ulcer patients with hospital verified gross hematemesis and/or melena, a mortality rate of less than 2 per cent. Three of 129 obstructed patients failed to respond to a described obstruction regimen.

4. Tincture of belladonna, in doses of 1.5 c.c. or more (or equivalent quantities of atropine), decreases the amount of antacid required to produce "free achlorhydria."

Addendum

Since submission of this manuscript for publication, an additional uncomplicated 141 duodenal and five gastric ulcers have been treated under the described regimen, except that Banthine,® 100 mg. every four hours, was substituted for tincture of belladonna. Eighty-nine became pain-free within 24 hours of initiation of therapy; 24 within two days; 11 within three days; eight within four days; five within five days; two within six days; three within seven days, and one each within nine, 10, 12 and 13 days. Comparison reveals that Banthine® relieves pain more promptly. Forty-eight demonstrable duodenal niches which could be roentgen-rayed weekly showed an average healing time of 1.9 weeks, or 13.3 days; and five gastric craters an average healing time of 2.2 weeks, or 15.4 days. We believe this reveals no statistically significant difference. There was less complaint of blurred vision and dry mouth with Banthine,® but four patients, only one with prostatism, had to be changed to tincture of belladonna because of severe urinary retention. Patients with obstruction complicating ulceration did better with tincture of belladonna, probably because Banthine® produced a greater depression of gastric motility.

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THE RECOGNITION AND TREATMENT OF HEPATIC AMEBIASIS *

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Hepatic amebiasis is a serious disorder and often it is not diagnosed. The variability and multiplicity of complaints frequently focus the clinician's attention on other disease entities. The process may be mild and the symptoms vague. The disease may be overlooked until the patient presents himself with a large liver abscess or other serious complications. Even then the diagnosis is sometimes not thought of until the patient is operated on or reaches the autopsy room. It is important that the diagnosis be made as early as possible, since delay in recognition results in an increase in morbidity and mortality.

The purpose of this report is two-fold. The first object is to emphasize certain important features that will help the clinician to recognize hepatic amebiasis, even in the presence of a normal stool and colon. The second object is to discuss the appropriate management of this disorder whatever the location of the primary lesion.

We have surveyed the experience in treating 28 patients having amebiasis during the past 12 years in the University Hospitals. We selected six cases from this group and one additional case from the Oakdale Tuberculosis Sanatorium to illustrate the many complicated problems encountered in making a diagnosis.

Case Reports

Case 1. A 25 year old white housewife was admitted to the University Hospitals on September 23, 1948, with a four year history of alternating diarrhea and constipation, attended by marked fatigue and a 30 pound weight loss. Two months prior to admission she had suddenly developed severe pains in the right chest, spiking fever to 103° F., shaking chills and a productive cough. Physical examination revealed an acutely and severely ill young woman who appeared moribund. She was having liquid bowel movements every 10 minutes and was expectorating copious amounts of chocolate-colored, tenacious sputum. The rectal temperature was 102.6° F., pulse rate 140, respiratory rate 32, blood pressure 120/60 mm. Hg, and weight 75 pounds. Her face and arms were a dirty bronze color. The right lung base was dull to percussion, with absent breath sounds, and râles were audible over the upper half of the right hemithorax. The liver was greatly enlarged and exquisitely tender.

Laboratory Data: The hemoglobin was 8.5 gm. per 100 ml., the erythrocyte count 3,300,000 and the white cell count 40,300 per cu. mm., with 89 per cent polymorphonuclear leukocytes. The liver function studies were slightly altered (table 1). The stools contained numerous motile trophozoites of *Endameba histolytica*. The sputum

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was negative for parasites, but a culture grew *Escherichia coli*. Following the intravenous injection of bromsulfalein, the sputum had a distinctly purplish hue and bile was noted in the sputum. A chest film showed marked elevation of the right leaf of the diaphragm to the level of the fifth interspace posteriorly (figure 1). The position of the right diaphragm was confirmed by pneumoperitoneum. One week after admission the hepatic abscess had drained sufficiently through a hepato-bronchopleural fistula so that a fluid level could be seen (figure 2).

The patient was treated immediately with emetine hydrochloride and diodoquin. Additional supportive therapy consisted of penicillin, whole blood, intravenous fluids and a highly nutritious diet. On the second day of therapy the patient's temperature rose to 105° F. On the third day her general condition improved, and thereafter she made a steady recovery and was discharged on the fifty-sixth hospital day. The emetine and diodoquin were repeated on two subsequent occasions at one month intervals.

TABLE I

The Effect of Amebic Hepatitis and Abscess on the Liver Function Studies of Case 1

	Sept. 1948	Oct. 1948	Nov. 1948	Dec. 1948	Sept. 1949	Oct. 1949	June 1950
Total protein	5.50	6.33	6.80	7.35	6.90	6.60	6.70
Albumin	2.86	3.39	3.70	4.83	4.54	3.83	4.58
Globulin	2.64	2.94	3.10	2.52	2.36	2.77	2.12
Ceph. floc.	24 hrs. 1+	....	24 hrs. 1+	....	....	24 hrs. 1+	24 hrs .neg.
	48 hrs. 3+		48 hrs. 2+			48 hrs. 2+	48 hrs. neg.
Thymol turb.	10.0	7.80	7.80	....	....	11.0	8.0
BSP*	....	40%	5%	....	....	....	2%
Zinc sulfate	....	10.6	....	15.5	....	7.0	9.0
Cholesterol	....	156	....	....	....	....	200
Alk. p'tase	....	8.8	....	3.6	....	....	1.6
Bilirubin**	....	....	....	....	....	0.75	0.75

The studies in September, 1948, were made during the height of the illness. The values of October, 1948, were obtained during the immediate recovery phase before the liver abscess had healed. The subsequent studies were made after a complete clinical recovery had been effected.

* BSP indicates sulfobromphthalein ("bromsulfalein") sodium.

** Serum bilirubin is measured in mg. per 100 c.c. by the indirect van den Bergh reaction

The patient was seen again in December, 1948, and September, 1949, at which times there was no evidence of relapse. Her most recent visit was on June 26, 1950, almost two years after the first admission. She was in excellent health and weighed 127 pounds. A chest film was normal except for minimal elevation of the right leaf of the diaphragm to the level of the eighth posterior rib and old pleural thickening in the right base (figure 3). A summary of the liver function studies over a 21 month period is recorded in table 1.

Case 2. A 24 year old white Army veteran entered the University Hospitals on May 23, 1950, with a history of recurring diarrhea three to four times a year which had begun in the South Pacific five years previously. Physical examination revealed a well developed, tired looking young man. The temperature, pulse and respiratory rate were normal. The blood pressure was 110/70 mm. Hg. The liver was tender to palpation and there was a faint bronzing of the skin over the forehead and forearms. Routine laboratory findings including complete blood count and urinalysis were within normal limits. The stools were negative for parasites. Sigmoidoscopic examination and x-rays of the colon were normal. Complement fixation test for amebiasis was positive. The patient was given a concurrent course of chloroquine

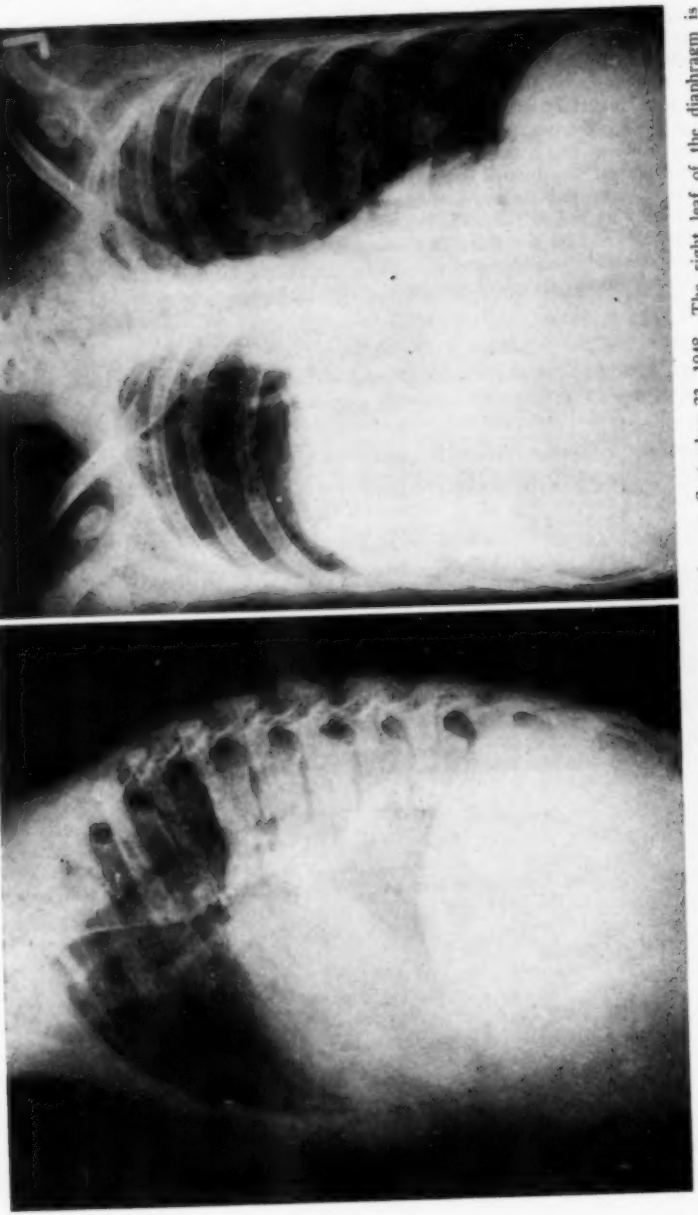

FIG. 1. (*Case 1.*) Posterior-anterior and lateral teleroentgenograms taken on September 23, 1948. The right leaf of the diaphragm is markedly elevated. The visualized portion of the right lung field is clear.

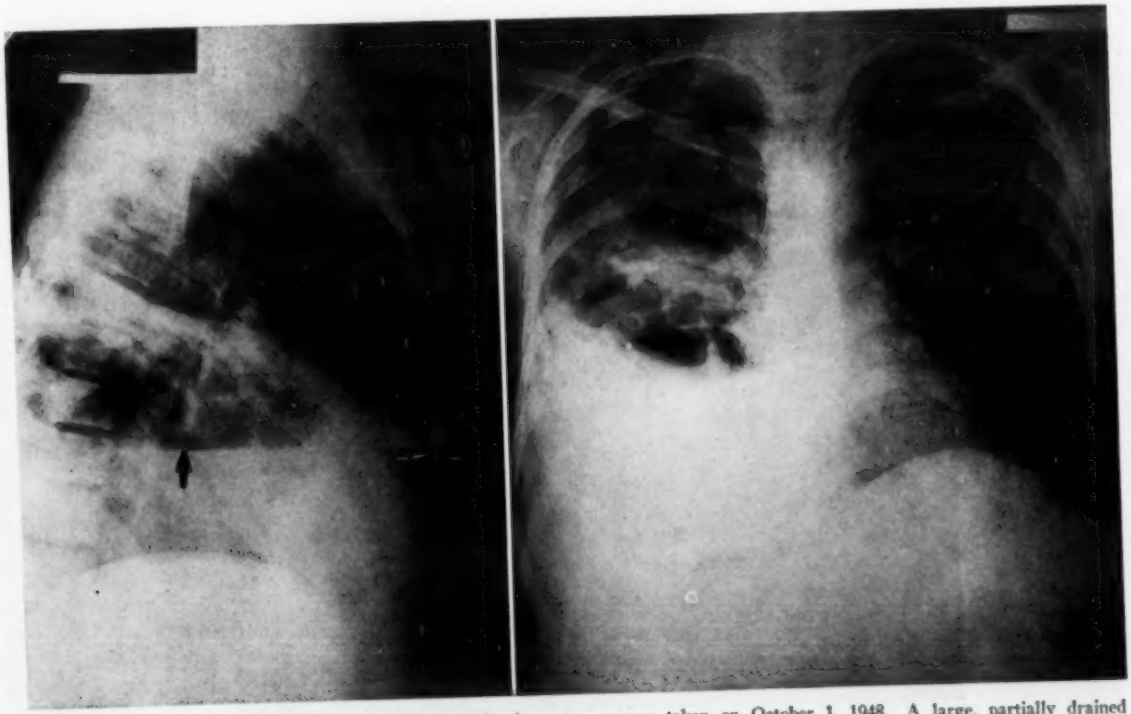

FIG. 2. (*Case 1.*) Posterior-anterior and lateral teleroentgenograms taken on October 1, 1948. A large, partially drained hepatic abscess is present; the fluid level is best seen in the lateral view (see arrow). The pleura at the right costophrenic angle is thickened.

and diodoquin. The liver tenderness disappeared, and he made a complete clinical recovery.

Case 3. A 31 year old white physician was seen in the out-clinic of the University Hospitals on May 10, 1950, complaining of chronic fatigue. He had been stationed in Germany with the U. S. Army during 1946–1947, and while overseas had experienced frequent rectal tenesmus. In 1949 he developed constipation, generalized malaise and afternoon temperature elevations. Many chest films were taken in a

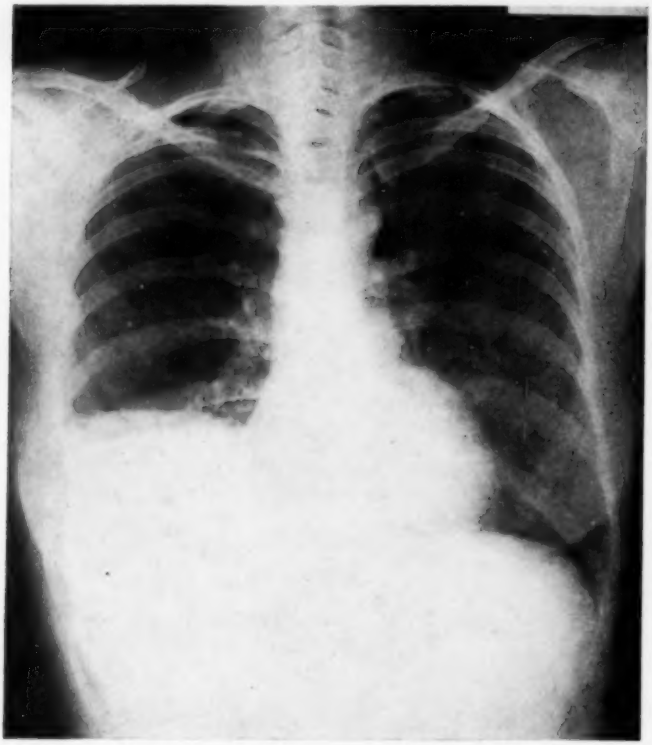

FIG. 3. (*Case 1.*) Teleroentgenogram of the chest taken on June 26, 1950. Some elevation of the right hemidiaphragm, old pleural thickening in the right lung base and obliteration of the right costophrenic angle remain.

search for tuberculosis, but no evidence of lung disease was discovered. In April, 1950, the patient experienced cramping lower abdominal pains. Physical examination revealed a chronically ill, tired and haggard patient. The temperature was 99.2° F., pulse rate 78, respiratory rate 18, blood pressure 125/75 mm. Hg, and weight 185 pounds. The skin of the face, hands, arms, thighs and abdomen (including pressure points) showed a coppery or muddy pigmentation. The liver was easily palpable and moderately tender. Routine laboratory findings, including complete blood count

and urinalysis, were within the accepted normal range. Examination of the stools revealed active motile trophozoites of *E. histolytica*. He was treated as an ambulatory patient. A course of diodoquin and chloroquine was given, and almost immediate improvement was noted. Liver tenderness disappeared and strength returned rapidly. Four months later there was no evidence of recurrence of the disease.

Case 4. A 24 year old feebleminded white man entered the University Hospitals on June 28, 1946, with a two month history of increasing weakness, unexplained anemia and afternoon fever. Two weeks prior to admission he had developed enlargement of the abdomen and leg edema. Physical examination revealed a chronically ill young man who had noticeable distention of the abdomen and pitting edema of the legs. The temperature was 101° F., pulse rate 120, respiratory rate 30 and blood pressure 120/70 mm. Hg. The right hemidiaphragm was markedly elevated. A slightly tender abdominal mass was readily palpated in the right upper quadrant extending below the umbilicus.

Laboratory Data: The hemoglobin was 7.0 gm. per 100 ml., the erythrocyte count 2,800,000 and the white cell count 20,000 per cu. mm., with 90 per cent polymorphonuclear leukocytes. The blood urea nitrogen and creatinine were normal. The serum bilirubin was 1.0 mg. per 100 ml. (indirect van den Bergh); the cephalin flocculation 3 plus in 24 hours and 4 plus in 48 hours; the total protein, 6.10, albumin, 1.81, and globulin, 4.29 gm. per 100 ml. An electrocardiogram and a colon series were normal. A chest film was normal except for elevation of the right half of the diaphragm. The stools were negative for parasites. Many independent examiners made a variety of diagnoses. Only one considered the possibility of hepatic amebic abscess. A huge amebic abscess of the liver was found on exploring the abdomen surgically, and five quarts of brown pus were drained with a trochar. The patient was then treated with emetine. Within two days his temperature returned to normal, and he made a rapid recovery.

Case 5. A 37 year old Negro slaughterhouse worker was admitted to the University Hospitals on December 6, 1945, with the chief complaint of severe pain in the right side of the abdomen of five weeks' duration. He gave a one year history of a 60 pound weight loss, increasing malaise, spiking temperature and constipation. Brucellosis was suspected, but agglutinations were negative. Physical examination revealed an emaciated and severely ill patient. The temperature was 101° F., pulse rate 124, respiratory rate 24 and blood pressure 110/60 mm. Hg. The right leaf of the diaphragm was elevated and fixed. There was an extremely tender, ill-defined mass in the right upper quadrant of the abdomen, with marked muscle guarding.

Laboratory Data: The hemoglobin was 9.5 gm. per 100 ml., the erythrocyte count 3,750,000, and the white cell count 36,150 per cu. mm., with 89 per cent polymorphonuclear leukocytes. Urinalysis showed a 1 plus albuminuria. The stools were never examined. The blood urea nitrogen and creatinine were within normal limits. The total protein was 6.50, albumin 2.42 and globulin 4.08 gm. per 100 ml. An x-ray of the chest showed clear lung fields, with elevation of the right hemidiaphragm. Intravenous pyelography revealed no urologic abnormalities, but there was a pocket of air in the right upper quadrant, representing an abscess cavity which was in communication with the gastrointestinal tract. On colon series the barium could be seen passing through a fistula from the hepatic flexure of the colon into the subphrenic abscess cavity, then via another fistulous tract into the duodenum (figure 4).

The clinical diagnosis was carcinoma of the colon with a subphrenic abscess and duodenal-colic fistula. Treatment consisted of three whole-blood transfusions, penicillin and insertion of a Miller-Abbott tube. On the tenth hospital day the abscess was drained surgically and a large amount of foul smelling, grayish pus was obtained. The patient's course was rapidly downward and he died on December 26,

1945. At post mortem there were multiple liver abscesses, a large subphrenic abscess extending along the right pericolic gutter, a duodenal-colic fistula communicating with the abscess cavity, and a large gangrenous appendix with localized pelvic peritonitis. Microscopic examination of the appendix, duodenal-colic fistula borders and the liver showed the presence of many trophozoites of *E. histolytica*.

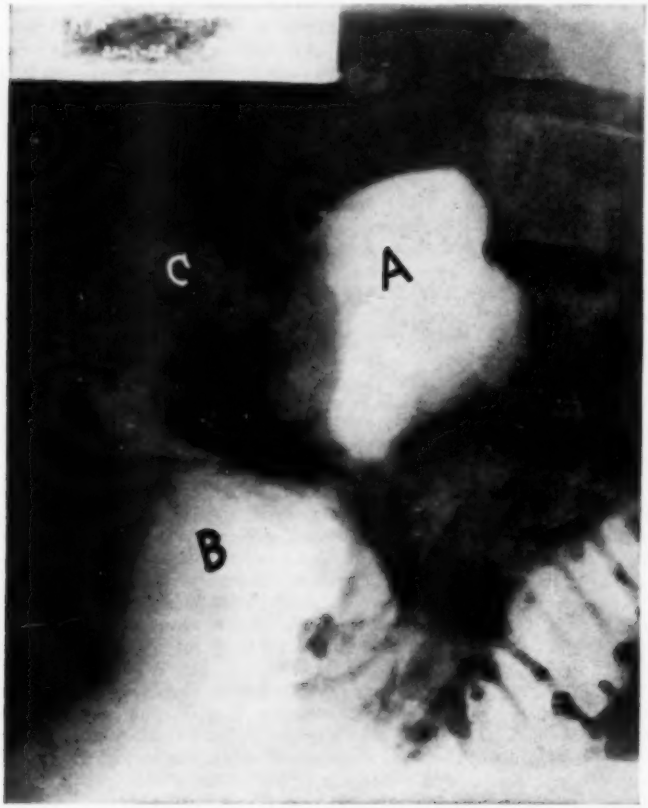

FIG. 4. (*Case 5.*) Colon series done on December 7, 1945. A spot film of the right upper quadrant clearly shows the abscess cavity which connects with the colon and duodenum by fistulous tracts; there is retrograde filling of the duodenum. "A" represents the duodenum, "B" represents the colon and "C" the abscess.

Case 6. A 53 year old white laborer entered the University Hospitals on February 24, 1940, with a two-month history of persistent bloody diarrhea, increasing weakness and a 40 pound weight loss. One month prior to admission he had developed pain in the right chest and a cough with production of brownish sputum. Physical examination revealed a moribund patient. The temperature was 101° F., pulse rate 130 and blood pressure 118/86 mm. Hg. There were dullness over the left

chest and signs of fluid up to the sixth rib posteriorly. The liver was enlarged and tender. A fungating mass could be palpated encircling the rectum 2 or 3 cm. above the anal sphincter. A clinical diagnosis of annular carcinoma of the rectum with metastasis to the right chest was made.

Laboratory Data: The hemoglobin was 8.0 gm. per 100 ml., the erythrocyte count 3,350,000 and the white cell count 15,000 per cu. mm. A chest film showed the right leaf of the diaphragm to be obscured by a dense shadow, which was interpreted as being encapsulated fluid in the right lung base (figure 5). The stools were not examined, sigmoidoscopy was omitted and a biopsy was not taken of the rectal mass. Thoracentesis yielded a large amount of brownish pus which was negative for organisms on direct smear and culture. The diarrhea persisted. The patient's condition deteriorated rapidly and he died on the eighth hospital day.

Postmortem examination revealed *E. histolytica* infestation of the large intestine, liver and right lung. There was extensive ulceration of the entire colon and rectum. A solitary amebic abscess the size of a fist was present in the liver and had eroded through the right chest, causing necrotic excavation of the lower lobe of the right lung. No evidence of carcinoma was present. The rectal mass consisted of an area of perirectal cellulitis with intervening bridges of puffy edematous mucosa between ulcerations.

Case 7. A 34 year old white businessman was admitted to the Oakdale Tuberculosis Sanatorium on August 15, 1950, with a seven year history of pulmonary tuberculosis. In 1947 he had developed intermittent griping lower abdominal pains associated with nausea and an occasional loose stool. During an attack of pain an appendectomy was performed, yet postoperatively the intermittent abdominal distress continued. In April, 1950, he developed an external ophthalmoplegia of the right eye, and three months later his right face was stiff. On August 1, 1950, he began passing four to five soft stools daily and experienced increasing pain in his right costal region. Physical examination revealed the patient to be critically ill. The rectal temperature was 103° F., pulse rate 120, respiratory rate 26, blood pressure 100/60 mm. Hg, and weight 65 pounds. His face had the appearance of a fading suntan. The liver was greatly enlarged and very tender to light percussion. There was an external ophthalmoplegia of the right eye, slight involvement of the eye rotators of the left eye, and a complete peripheral facial paralysis (Bell's palsy) on the right. The right epididymis was hard and nontender. The prostate was enlarged, soft and tender.

Laboratory Data: The hemoglobin was 8.0 gm. per 100 ml., the erythrocyte count 3,000,000 and the white cell count 6,000 per cu. mm., with a normal differential count. The sedimentation rate was 24 mm. in one hour. The urine contained an occasional pus cell. The serum bilirubin was 0.75 mg. per 100 ml. (indirect van den Bergh). The thymol turbidity was 6 units and the cephalin flocculation was negative in 24 and 48 hours. Repeated examinations of the stools were negative for pathogens. A sigmoidoscopic examination was entirely normal up to 20 cm. Fluoroscopy of the chest revealed moderate elevation and 75 per cent reduced mobility of the right half of the diaphragm. The costophrenic angles were clear. A chest film showed old fibrotic disease which had not changed appreciably since 1943. Sputum studies were positive for acid-fast bacilli (Gaffky II–IV). Intravenous pyelograms and gastrointestinal series, including a motor meal, were normal. A colon series was interpreted as normal, but much difficulty was had in filling the cecum. A lumbar puncture revealed normal pressures, including dynamics; clear spinal fluid; no cells; 2 plus Pandy; normal chemistries except for an elevated protein of 72 mg. per 100 ml., and a negative culture for tubercle bacilli. Complement fixation test for amebiasis returned "strongly positive" (U. S. Public Health Service, Communicable Disease Center, Atlanta, Georgia).

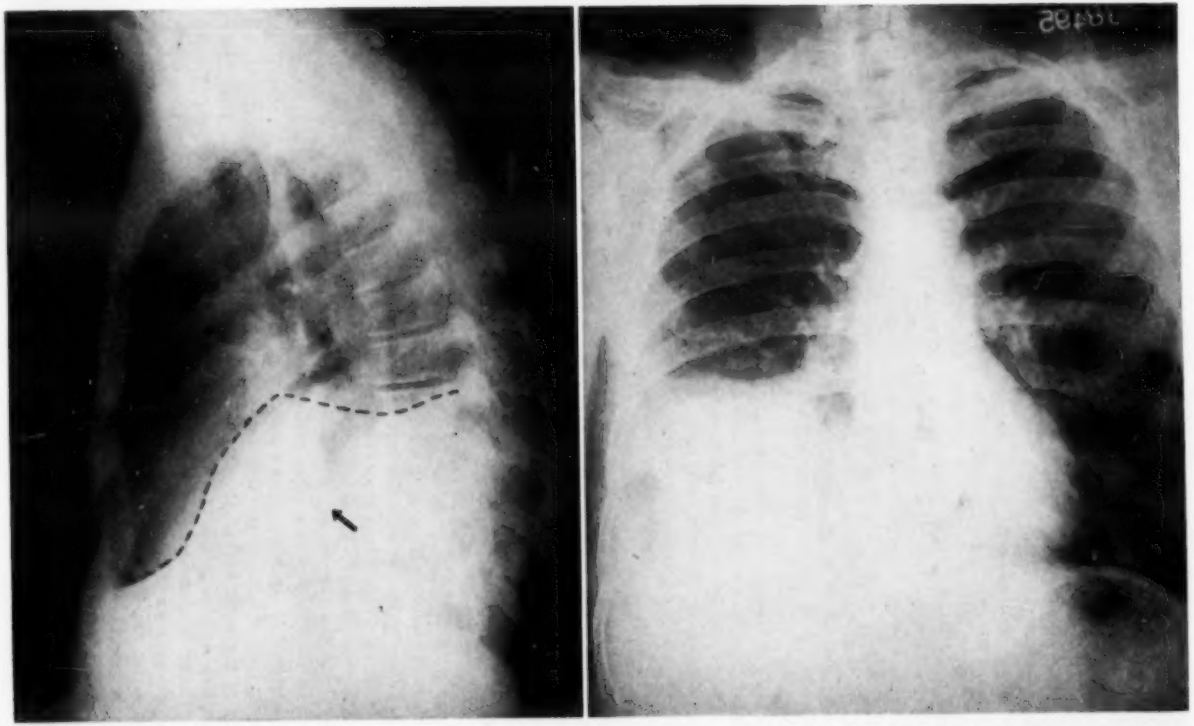

FIG. 5. (*Case 6.*) Posterior-anterior and lateral teleroentgenograms taken on February 24, 1940. The right hemidiaphragm is obscured by a dense mass on the posterior-anterior film. The lateral view shows involvement of the lower lobe (see dotted lines). The arrow points to the posterior cardiac silhouette. Necrotic excavation of the right lower lobe was present on postmortem examination.

The patient was placed on dihydrostreptomycin 1.0 gm. daily by intramuscular injection. He was given aureomycin, 750 mg. every six hours by mouth for one week, but had no response. He continued spiking a temperature to 100 to 102° F. and remained acutely ill. The aureomycin was then discontinued and chloroquine diphosphate ("Aralen") started. Within 12 hours his temperature returned to normal (figure 6), and within 72 hours the liver was smaller and less tender. The liver gradually receded to normal size, and normal movements of the diaphragm were noted on subsequent fluoroscopic examinations. Diodoquin was started on the fourth day of chloroquine therapy. We gave additional supportive therapy, including four whole-blood transfusions. Five weeks after specific amebacidal therapy the complement fixation test reverted to negative.

The temperature remained normal for five days, when daily spikes recurred to 100 to 101° F. During October the patient developed a stiff neck, nausea and vomiting and became confused. There was an insidious progression of neurologic

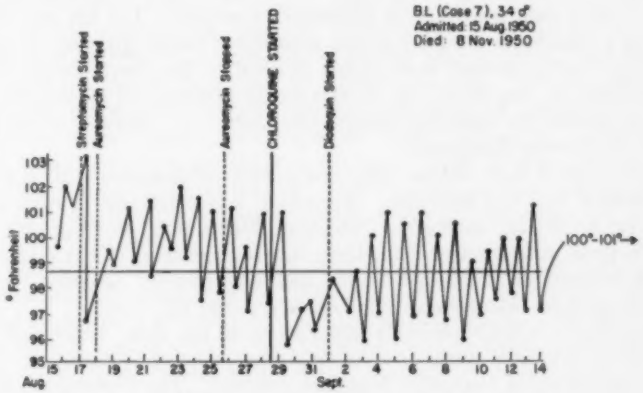

FIG. 6. (*Case 7.*) Drug and temperature chart on case 7.

findings involving the eye rotators. A repeat lumbar puncture revealed an initial pressure of 100 mm. water; normal manometrics; 3 plus Pandy; a total protein of 228 mg., sugar 40 mg. and chlorides 650 mg. per 100 ml. The spinal fluid culture was negative for tubercle bacilli or other pathogenic organisms.

We made a diagnosis of amebic hepatitis, which had responded satisfactorily to treatment, and disseminated tuberculosis with tuberculoma of the pons and tuberculous meningitis.

A partial postmortem examination revealed tuberculomas of the liver, spleen and kidneys. There was a tuberculous peritonitis, epididymitis, prostatitis, and involvement of both vasa deferentia. The adrenal glands were entirely destroyed, being present as large caseous masses. The bowel at the ileocecal junction was bound down by old adhesions but was otherwise normal. Tuberculous involvement of the lungs was minimal. The liver, except for an occasional small tuberculoma not over 10 mm. in diameter, was normal in size, shape and appearance. There was no evidence of healing of the tuberculomas.

Discussion

Diagnostic Aids: There are important features exemplified by these seven cases which are helpful in diagnosing hepatic amebiasis.

(1) An enlarged, tender liver is a common and significant physical finding, and whenever it is encountered one should think of hepatic amebiasis in the differential diagnosis. Ninety-five per cent of 184 patients with amebic abscess of the liver studied by Banker [1] had tender livers, and 83 per cent had definite liver enlargement. Particular attention should be directed to careful palpation of the abdomen and percussion of the liver.

Liver tenderness may be overlooked easily unless the epigastrium is palpated with the fingers pressed beneath the right costal margin near the midline. Even though the liver is not demonstrably enlarged, pressure of the fingers on the falciform ligament at the height of deep inspiration produces a sharp pain which might otherwise be missed. The left side should serve as a control for comparing pain sensation. In known cases of amebic dysentery among soldiers in an Army hospital in the South Pacific during World War II, one of us (H. E. H.) found this method of palpation extremely valuable in detecting hepatic amebiasis. As recovery takes place, hepatic tenderness disappears.

Even with a large tender liver, one cannot differentiate amebic abscess from amebic hepatitis clinically. Therefore, it is preferable to refer to the condition as hepatic amebiasis. Hepatic abscess may be suspected when there is great enlargement of the liver, marked elevation of the diaphragm, a high intermittent fever and severe systemic reaction. Amebic hepatitis is more common than abscess (e.g., cases 2, 3 and 7).

(2) Dirty, copper-colored pigmentation of the skin, which has been likened to a fading suntan, is an important clinical feature. It should arouse suspicion of low-grade hepatic amebiasis. The distribution of this pigmentation on the face and forehead makes it resemble the mask of pregnancy. Often the flexor surface of the wrists, body pressure points and skin creases are pigmented also. Loeber and D'Antoni [2] were impressed with the frequency of these skin changes in a series of 73 children with amebiasis seen in office practice. Three typical cases of hepatic amebiasis presented in their report had a peculiar muddy, sallow complexion in addition to a large tender liver.

(3) Often fluoroscopy of the chest is helpful. Elevation and fixation of the right leaf of the diaphragm point to underlying disease in the liver, with hepatic enlargement or subdiaphragmatic abscess. Sometimes there is blunting of the right costophrenic angle and haziness in the base of the lung from compression atelectasis or pleural effusion.

(4) Liver function tests are important in the diagnosis of hepatic amebiasis. Even with advanced liver abscess, as in case 1, abnormalities in liver function may be slight (table 1). Occasionally there is some decrease in bromsulfalein clearance, reversal in the A/G ratio or a positive

cephalin flocculation test. The opposite is true in infectious hepatitis, where liver function may be seriously impaired while the physical findings are few and mild.

(5) A complement fixation test may be a valuable adjunct in helping the clinician to substantiate the diagnosis of hepatic amebiasis.[3] One of the chief difficulties in the past has been to develop a suitable antigen. Using commercial materials, Hussey and Brown [4] reported positive tests in 82.3 per cent of 17 cases with hepatic amebiasis. This high percentage is not found in intestinal amebiasis, where the percentage of positive reactions is much lower. Samples of serum * for testing may be sent by air mail to the U. S. Public Health Service, Communicable Disease Center, Laboratory Services, 291 Peachtree Street, Atlanta, Georgia. This public health laboratory and others are trying to evaluate the results of complement fixation tests for amebiasis in a large series of cases throughout the country.

(6) With a positive complement fixation test, a therapeutic response and a fall in the titer of positive sera following specific amebacidal therapy, a presumptive clinical diagnosis of hepatic amebiasis is confirmed even though the colon is normal to careful sigmoidoscopic examination and biopsy, and stool examination is negative. The presence of amebae in the liver without coexisting lesions in the bowel is more common than is generally recognized. In 1947, Banker [1] reported on 66 cases of amebic abscess of the liver diagnosed at autopsy. Of these, 15 (23 per cent) had no evidence of intestinal lesions.

Criteria for making a diagnosis of amebic hepatitis are not always clear cut. Occasionally more than one disease complicates the picture. Case 7 had amebic hepatitis in addition to widespread tuberculosis with destruction of the adrenal glands. Following combined therapy with chloroquine and diodoquin, his liver returned to normal size and the complement fixation test changed from strongly positive to negative. These two facts led us to make a diagnosis of amebic hepatitis. His temperature was normal and he improved for several days, only to have recurrence of fever and to take a steady downward course. It is improbable that the few small tuberculomas of the liver caused the enlargement and tenderness of the liver. Addison's disease was not suspected before the postmortem examination, but should have been considered in the differential diagnosis. One cannot

* At least 5 c.c. of serum are required. Using a clean, sterile, dry needle and syringe, draw a specimen of blood before breakfast or at least three hours after the last meal to avoid a chylous specimen. The blood is allowed to clot at room temperature (one to two hours), then placed in the refrigerator to retract the clot. The serum is drawn off from the clot with a sterile pipette and rendered perfectly free of red cells by centrifugation in a sterile dry tube, 0.02 c.c. of 3 per cent *aqueous* solution of borated merthiolate per c.c. of serum may be added to prevent bacterial growth. Indicate on the tube label if merthiolate has been added (3 gm. powdered Merthiolate Lilly, 1.4 gm. borax and 100 c.c. distilled water.) Make fresh solution every 30 days and keep stored in the refrigerator. Do not heat the serum; this inactivates it. Enclose a brief statement regarding the patient's illness with the serum specimen. The tubes containing serum for shipment should be properly sealed with rubber stoppers or screw tops to prevent leakage. Label properly for identification and wrap carefully to prevent breakage.

determine whether the facial pigmentation was caused by chronic amebic hepatitis or adrenal insufficiency.

Treatment: Vioform, chiniofon * and diodoquin are nonabsorbable halogenated quinoline derivatives which have a local amebacidal action in the bowel wall but are ineffective against extraintestinal amebiasis. In addition, Carbarsone, Wia † ("Milibis") and two new thioarsenite derivatives of carbarsone oxide make up the chief arsenical intestinal amebacides. In our experience, diodoquin has proved to be the most efficacious of this group of drugs. According to preliminary reports, the thioarsenites show promise.[5, 6] D'Antoni [7] reported good results with diodoquin in 1943. We have had excellent results with diodoquin *when it is combined with emetine or chloroquine,* and can find no evidence that other forms of therapy are of greater efficacy than combined therapy in the treatment of amebiasis.

Prior to the introduction of chloroquine diphosphate, emetine hydrochloride was the only drug available for the treatment of extraintestinal amebiasis. In spite of the high specificity of emetine for amebic hepatitis and abscess, it was notoriously poor in treating intestinal amebiasis. It is toxic and has a cumulative action, so it must be administered with care. The patient must be kept in bed to help prevent hypotension, syncope and other alterations of cardiovascular function. Some patients become "emetine-fast" and do not respond to the drug. When one uses emetine, diodoquin should be given concurrently.

Chloroquine's high therapeutic effect and lack of toxicity render it superior to emetine. It is the drug of choice for treatment of extraintestinal amebiasis. In 1948, Conan [11, 12] observed prompt clearing of signs and symptoms in 12 cases of amebic hepatitis treated with chloroquine; one of the patients cured had previously failed to respond satisfactorily to emetine. Chloroquine, though specific for amebic hepatitis and amebic liver abscess, effects a cure in no more than 50 per cent of the cases with intestinal amebiasis.

Frequently an unrecognized hepatitis coexists with intestinal amebiasis. The clinician should give a nonabsorbable drug, preferably diodoquin, to attack locally the primary source in the bowel, and *at the same time* an absorbable drug, preferably chloroquine, to exert its maximal effect on the liver and other sites of metastatic extension. Combined therapy with chloroquine and diodoquin has the distinct advantage of permitting treatment of many patients on an ambulatory basis, as in case 3.

Favorable reports of the value of aureomycin and terramycin in treating intestinal amebiasis are appearing. McVay, Laird and Sprunt [8] are very enthusiastic as a result of having treated 37 patients with aureomycin. Their only failure was a complicated case with amebic liver abscess. Hughes [9] gave aureomycin to 38 patients and reports that 27 were com-

* Trade names "Yatren 105" and "Anayodin."

† Has the chemical formula bismuthoxy p-N-glycolylarsanilate; also studied under the designation of Winn 1011.

pletely cured. One patient with hepatitis was thought to be cured, while another with hepatitis showed no improvement. Our experience with aureomycin is limited to one patient (case 7), in whom it was ineffective; no improvement occurred until chloroquine was given. Most and Van Assendelft [10] gave terramycin to 22 patients with amebic colitis, and the stools of all but one were freed of parasites. Aureomycin and terramycin have not yet had adequate clinical trial.

The amebacidal drugs discussed are listed in table 2; the routes of administration and adult dosages are given. One group of drugs is effective primarily against intestinal amebiasis, the other against extraintestinal amebiasis.

It has been pointed out that secondary infection may play an important rôle in metastatic lesions and in extensive colitis with pericolic or perirectal abscesses. In 1946, Hargreaves [13] cited his experience in treating an

TABLE II

Amebacidal Drugs, Showing Routes of Administration and Adult Dosages. One group of drugs is effective against intestinal amebiasis and the other group against extraintestinal amebiasis

Drug	Route of Administration	Adult Dosage	Phase of Amebiasis Effected
Diodoquin	Oral	630 mg. (3 tabs.) t.i.d. × 20 days	Intestinal
Aureomycin	Oral	500 mg.q. 6 hr. × 7 days	Intestinal
Terramycin	Oral	250–500 mg.q. 6 hr. × 10 days	Intestinal
Emetine	Intramuscular	0.065 gm. (1 gr.) daily × 7–10 days	Extraintestinal (hepatic)
Chloroquine (Aralen*)	Oral	1.0 gm. (4 tabs.) daily × 2 days, then .05 gm. × 19 days	Extraintestinal (hepatic)

* A proprietary name of chloroquine diphosphate.

invalid British soldier from India who did not respond to amebacidal drugs until penicillin was started. In 1949, Armstrong, Elsdon-Dew and Marot [14] in a large series of cases observed that penicillin and sulfasuxidine increased the effect of the amebacidal drugs. We used penicillin in addition to specific therapy in case 1 because of secondary infection; a hepato-bronchopleural fistula was present, and the sputum culture grew *E. coli*. Such patients usually develop septicemia and die if not treated properly.

Evaluation of Therapy: We reviewed the treatment of 28 patients with proved amebiasis admitted to the University Hospitals from 1938 through July, 1950. All except two patients (cases 2 and 4) had intestinal lesions and parasites in the stools, and six had liver abscesses. Two (cases 5 and 6) were undiagnosed and had no specific treatment. Fifteen were treated with intermittent or alternating therapy, using one of the iodides or emetine. Eleven were treated with combined therapy, using emetine and an iodide

TABLE III

A Review of the Treatment of 28 Patients with Amebiasis Admitted to the University Hospitals, Iowa City, Iowa, from 1938 through July, 1950

No. Cases	Treatment	Results
2	None	2 deaths
15	Intermittent or alternating	7 relapses (3 patients)
11	Combined	0 relapses

(eight patients) or chloroquine and diodoquin (three patients). The results were significant (table 3). The two untreated patients died from metastatic complications. Three of the patients in the group receiving intermittent or alternating therapy had relapses: one with intestinal amebiasis returned in five months with a large liver abscess, and the other two patients each returned three times in less than three month intervals with recurring bowel lesions. There were no relapses in the group treated with combined therapy. Relapses are known to occur using combined therapy, but they are uncommon. In the event of a relapse, therapy must be repeated.

SUMMARY AND CONCLUSIONS

Seven cases of hepatic amebiasis are reported. Helpful diagnostic aids are (1) tender and often enlarged liver; (2) fading suntan complexion of the skin; (3) elevation or fixation of the right leaf of the diaphragm; (4) little or no change in liver function tests; (5) positive complement fixation test, with a fall in titer following specific amebacidal therapy, and (6) specific therapeutic response.

Vioform, chiniofon, diodoquin, carbarsone, Milibis and two new thioarsenite derivatives of carbarsone oxide comprise the main list of amebacidal drugs which have a local action upon contact with the bowel wall. Favorable reports are appearing regarding aureomycin and terramycin, though they have not yet had adequate clinical trial. Chloroquine and emetine are the two drugs available for the treatment of extraintestinal amebiasis; both drugs are specific for amebic hepatitis and abscess. Chloroquine's high therapeutic effect and lack of toxicity render it superior to emetine. Chloroquine should always be given *in combination with one of the local amebacidal drugs,* preferably diodoquin. Secondary infection should be treated with the appropriate antibiotic.

The treatment of 28 patients with amebiasis admitted to the hospital from 1938 through July, 1950, is reviewed. Two untreated patients died. Three out of a group of 15 patients treated with intermittent or alternating therapy had a total of seven relapses. There were no relapses in the group which received *combined therapy.*

ACKNOWLEDGMENT

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MYOCARDIAL LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS *

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Recently Saphir, Katz and Gore [1] stressed that the myocardial lesions in subacute bacterial endocarditis may be of more than academic interest. With the possibility of eliminating the infecting organisms by the use of the antibiotics, the myocardium comes into focus as a potential source of cardiac failure in the patient who responds satisfactorily from the point of view of infection.

The primary purposes of the study here reported were to determine the nature and frequency of myocardial lesions in cases in which the patients had died of subacute bacterial endocarditis, and to ascertain the effect of penicillin therapy upon the lesions as judged from the material in the pathologic collection of the Mayo Clinic.

Historical Review

According to Saphir, Bracht and Wächter in 1909 injected streptococci obtained from patients who had died of acute infectious diseases into rabbits, and then were able to demonstrate areas of myocardial necrosis surrounded by lymphocytes, fibroblasts and giant cells. Other types of lesions were also described, including circumscribed areas of cellular infiltration in the interstitial tissue, and collections of lymphocytes, fibroblasts and plasma cells. It is as a result of this work that myocardial lesions in subacute bacterial endocarditis have come to be known as "Bracht-Wächter bodies." A variety of lesions are designated by this name, however. Libman [2] in 1923 referred to the Bracht-Wächter bodies as cellular interstitial infiltrates. The same author, in 1927, in collaboration with Rothschild and Sacks [3] referred to the Bracht-Wächter bodies as "focal lesions consisting of cellular infiltration 'chiefly round cells' in areas where the muscle fibers have undergone degeneration or necrosis." Gross and Fried [4] said that Bracht-Wächter bodies were mild interstitial mononuclear infiltrations, which were occasionally focal. Boyd [5] described them as small collections of polymorphonuclear leukocytes around necrotic material, and Bell [6] called them small abscesses with or without central necrosis or giant cells.

Coombs [7] in 1922 stated that the myocardial lesions in streptococcal endocarditis were nearly always obviously emboli. In 1926 Clawson and

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Bell [9] found active inflammation in 14 hearts from 61 cases of subacute bacterial endocarditis. Thayer [9] described acute myocarditis in 14 of 23 cases. In 1929 Clawson [10] stated that in his experience myocarditis was more common in subacute bacterial endocarditis than in either acute or chronic rheumatic endocarditis.

In 1935 Saphir [11] reviewed the literature and reported on 35 cases of subacute bacterial endocarditis studied personally, particularly with reference to the myocardial lesions. The lesions he described were petechial hemorrhages, acute inflammatory changes with foci of necrosis and abscess formation, minute infarcts, perivascular cellular infiltrations, Aschoff bodies and perivascular fibrosis. He reported that the organizing infarct was the most characteristic change in the myocardium in this disease. De Navasquez,[12] in 1939, reported having found intravascular lesions, frequently containing bacteria, in 16, and extravascular lesions in the myocardium in 19 of 20 cases of subacute bacterial endocarditis. The extravascular lesions were foci of polymorphonuclear leukocytes, with or without necrosis of some myocardial cells in the vicinity.

Saphir,[13] in 1946, described a granulomatous lesion in subacute bacterial endocarditis, in addition to the Aschoff body. This he called a "foreign body granuloma," caused by response to calcium in emboli that had become impacted in the small vessels of the heart. He has found these only in cases in which the patient had been treated either with a sulfonamide or with penicillin.

Material and Methods

This study is based upon 52 cases of subacute bacterial endocarditis of which the hearts are in the pathologic collection of the Mayo Clinic, representing material accumulated during the period 1923 to 1948, inclusive. Microscopic sections used were those secured at the time of the necropsy, supplemented in some instances by additional sections prepared from the gross specimens for this study. The number of sections studied per case varied from one to 15. Nine of the patients had received treatment with penicillin, in at least ordinary therapeutic doses. In five of these cases the results were considered clinically as "cures." In the discussion to follow, the patients that had received penicillin will be referred to as the "treated" patients, and those that had not received penicillin will be referred to as the "untreated" patients. For a case to qualify for inclusion in this series, the disease must have been of at least two months' duration, and characteristic vegetations of subacute bacterial endocarditis must have been found at necropsy. In 48 of the cases, at least one positive blood culture had been obtained during life. In another case, positive bacteriologic results depended on observing gram-positive streptococci in a smear prepared from a valvular vegetation. Among the treated patients, however, there were three in whom a positive blood culture was not obtained, and in two of these it was impossible to determine definitely the duration of the disease.

Observations

Forty-three untreated patients who had subacute bacterial endocarditis and nine treated patients were studied. Of the whole group of 52 patients, the ages varied from five to 76 years, the average age being 38.9 years. Thirty-two patients were female and 20 male. Twenty-four of the entire group gave a history of rheumatic fever, and in two others the history was suggestive of that disease.

Twenty-three patients of the untreated group had had clinical evidence of cardiac decompensation. Eight of the nine patients in the treated group had congestive cardiac failure.

Gross Pathologic Observations. Untreated Group: In 21 of the 43 cases, old or recent rheumatic valvulitis was diagnosed at the time of necropsy. There was a bicuspid aortic valve in three of the cases, in two of which aortic coarctation was associated. In one case, that of the child aged five years, there was a congenital communication between the left ventricle and the right atrium. The details of the malformation in this case were reported in an earlier communication.[14] In two cases there was a congenital membranous ventricular septal defect.

The vegetations of subacute bacterial endocarditis were present on the aortic valve alone in seven cases; on the mitral valve alone in 16 cases; on both mitral and aortic valves in 13 cases; on the mitral and pulmonary valves in one case; on the tricuspid valve in one case; and on the mitral, aortic and tricuspid valves in one case. In four cases the vegetations did not involve the valves. In many instances foci of the mural endocardium were involved.

The myocardium usually presented no specific gross picture. In several cases yellowish streaking was observed as well as minute hemorrhagic or yellowish spots.

Treated Group: In five of the nine hearts there was evidence of rheumatic endocarditis. In one case there was syphilitic involvement of the aorta.

The subacute bacterial endocarditic process involved the aortic valve alone in three cases, the mitral valve alone in four cases, and both the mitral and aortic valves in two cases. The gross appearance of the myocardium was in no way different from that of the untreated group.

Microscopic Observations. Both Groups: Lesions of the myocardium were found by microscopic examination in 42 of the 43 untreated patients. The one exception was the case of the child with the congenital communication between the left ventricle and the right atrium, with the vegetations of subacute bacterial endocarditis confined to the leaflets of the tricuspid valve and to the mural endocardium of the right ventricle. Microscopic lesions were found in all nine of the treated patients.

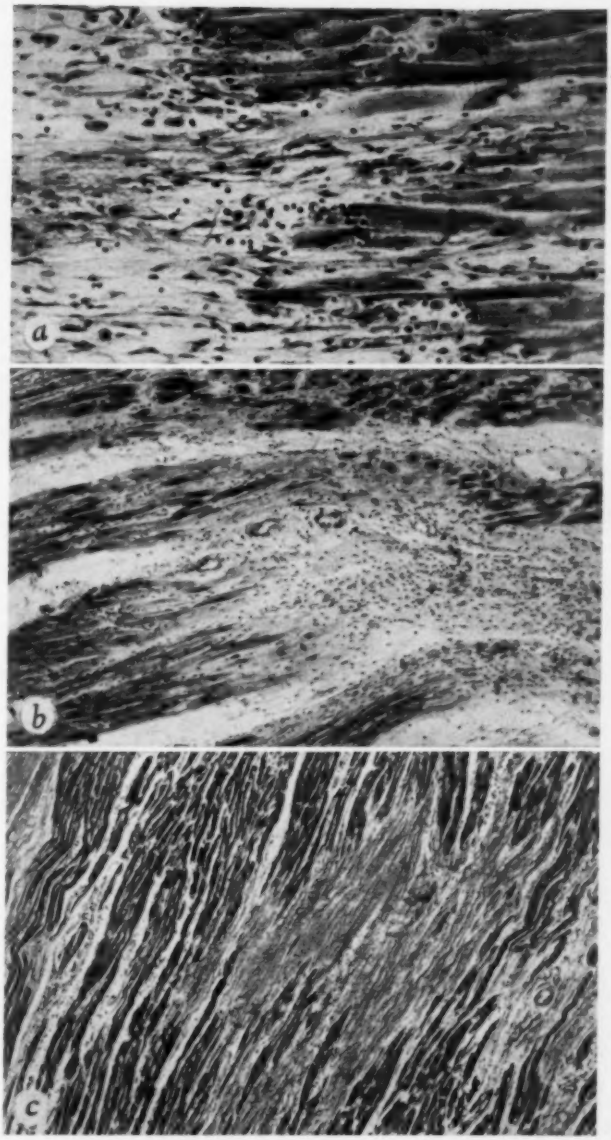

FIG. 1a. Healing myocardial infarct. Toward the left of the illustration, the muscle fibers have disappeared, leaving the stroma and a few phagocytic cells (hematoxylin and eosin × 150). *b*. Healed myocardial infarct. There is a scar containing some macrophages (hematoxylin and eosin × 70). *c*. Old healed myocardial infarct characterized by a dense, relatively acellular scar (hematoxylin and eosin × 50).

Microscopic lesions found were of the following types:

1. Miliary infarcts
2. Nonspecific inflammatory exudates
   a. Interstitial
   b. Perivascular
3. Aschoff nodules
4. Vascular lesions
   a. Emboli or thrombi
   b. Angiitis
5. Perivascular fibrosis
6. Petechiae
7. Foreign body granuloma

The miliary infarcts were subdivided into three catagories. *Recent* infarcts were characterized by areas of necrosis of myocardium with loss of nuclei and infiltration by polymorphonuclear leukocytes, and occasional erythrocytes. *Healing* infarcts consisted of areas of necrosis of muscle and also areas in which muscle fibers had been and were being removed by macrophages (figure 1*a*). These still showed a polymorphonuclear leukocyte response, along with lymphocytes and macrophages. Fibroblasts and capillaries could be seen beginning repair of the lesion, and during this stage minimal collagen production was at times evident. *Healed* infarcts usually showed complete replacement of the involved myocardium by dense fibrous connective tissue, with well-formed capillaries and a variable number of lymphocytes and pigment-containing macrophages (figures 1*b* and 1*c*).

Nonspecific inflammatory exudates were subdivided according to their location and their type. Location was either interstitial or perivascular. The character of the exudate determined the type. *Acute* lesions were characterized by infiltration of the interstitial or perivascular tissues predominantly by polymorphonuclear leukocytes (figures 2*a*, 2*b* and 2*c*). In some areas micro-abscesses were present (figure 2*d*). The *chronic* inflammatory lesions consisted of infiltration of the interstitial or perivascular tissue with lymphocytes, plasma cells and macrophages. Polymorphonuclear leukocytes were only occasionally found in such lesions.

Aschoff nodules fulfilled the criteria outlined by Gross and Ehrlich (figures 3*a* and 3*b*).

Emboli or thrombi appeared either bland or infected, the former predominating (figure 3*c*). Some were accompanied by an inflammatory response in the vessel wall and perivascular tissue, while others showed no evidence of reaction. There were a few instances of frank acute inflammation of the whole vessel wall, with or without associated emboli. When no emboli were present these lesions were classified as angiitis (figure 3*d*).

Perivascular fibrosis referred to an unusually large collar of fibrous connective tissue surrounding a vessel (figure 4*a*). Ordinarily, though not

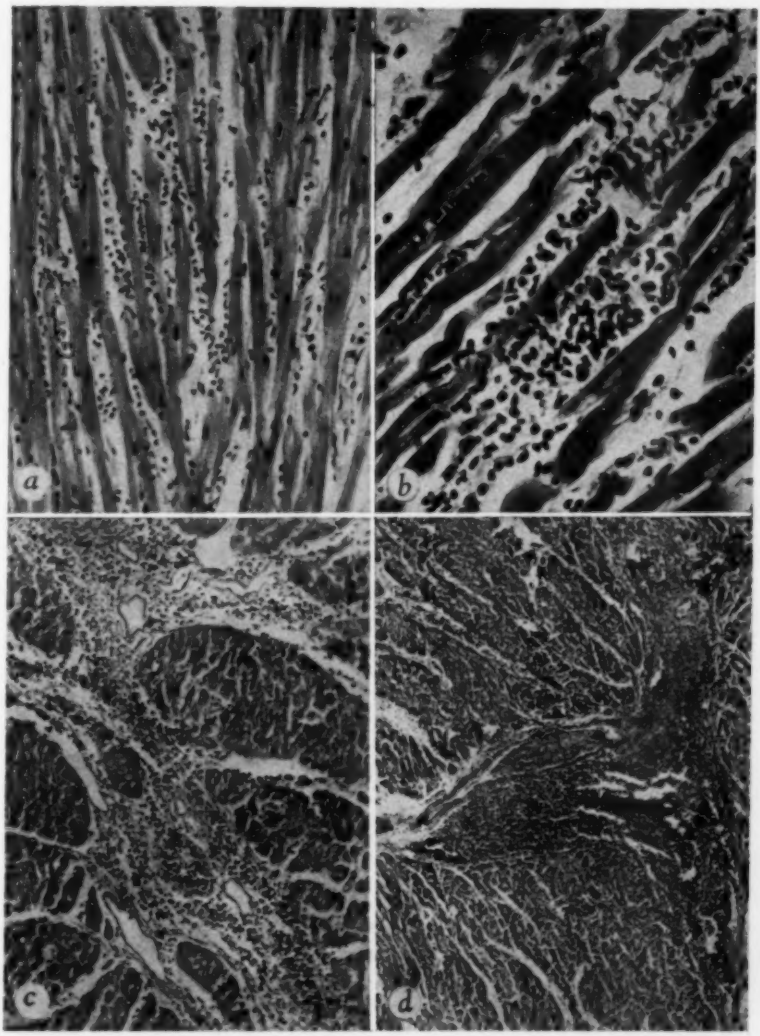

FIG. 2*a*. Acute interstitial myocarditis. The muscle fibers are separated by fluid and infiltration of polymorphonuclear leukocytes (hematoxylin and eosin × 165). *b*. Acute interstitial myocarditis. Necrosis of muscle fibers and infiltration of polymorphonuclear leukocytes and macrophages (hematoxylin and eosin × 300). *c*. Acute interstitial myocarditis. Heavy cellular infiltration within the connective tissue between the muscle bundles (hematoxylin and eosin × 120). *d*. Interstitial abscess. Beside a small artery containing an embolus there is an abscess between muscle bundles (hematoxylin and eosin × 55).

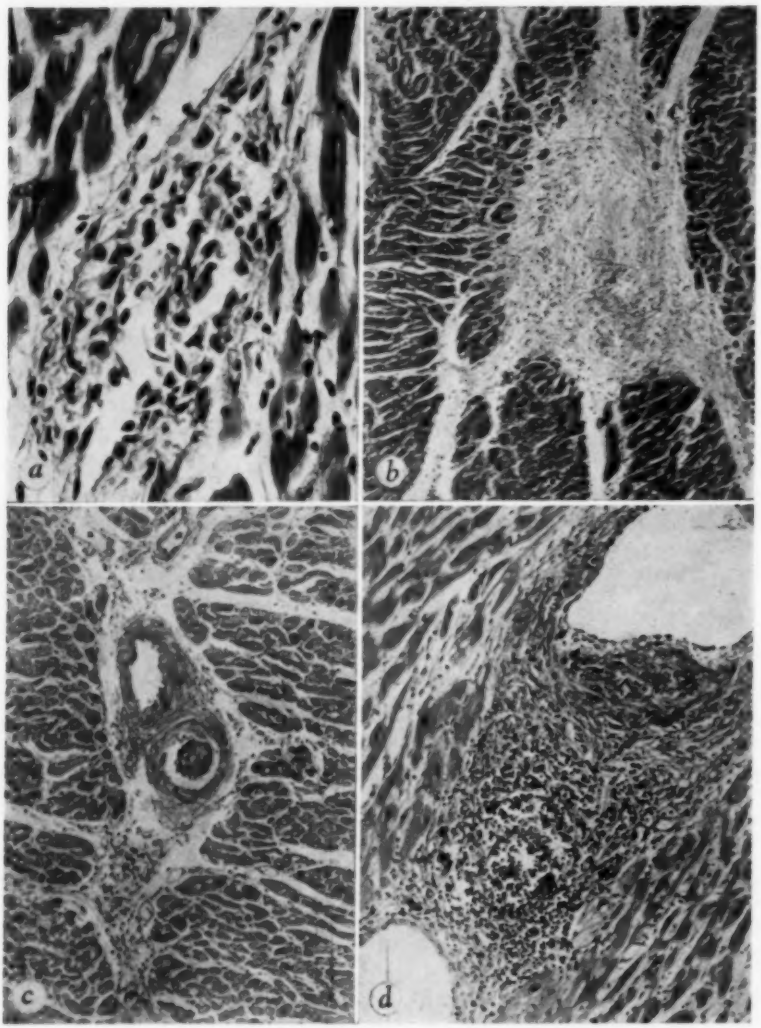

FIG. 3*a*. Aschoff body (hematoxylin and eosin × 400). *b*. Cellular myocardial scar suggestive of a healing Aschoff body (hematoxylin and eosin × 75). *c*. An embolus in a small coronary artery (hematoxylin and eosin × 120). *d*. Acute angiitis. A small coronary blood vessel and supporting connective tissue heavily infiltrated with leukocytes (hematoxylin and eosin × 120).

invariably, this was eccentric with respect to the vessel. An occasional lymphocyte, macrophage or plasma cell was present in the fibrous tissue.

Petechial hemorrhages were encountered in only one case. In this case there were numerous areas of exudation of erythrocytes among the muscle fibers, without evidence of inflammatory response or necrosis of muscle.

Microscopic lesions in the treated series were indistinguishable from those in the untreated series except for the addition of a lesion which was encountered in one of the treated patients. This was like the lesion which Saphir called a "foreign body granuloma." It consisted of an embolus containing calcified material, with a surrounding reaction of foreign body giant cells, histiocytes and lymphocytes (figure 4*b*).

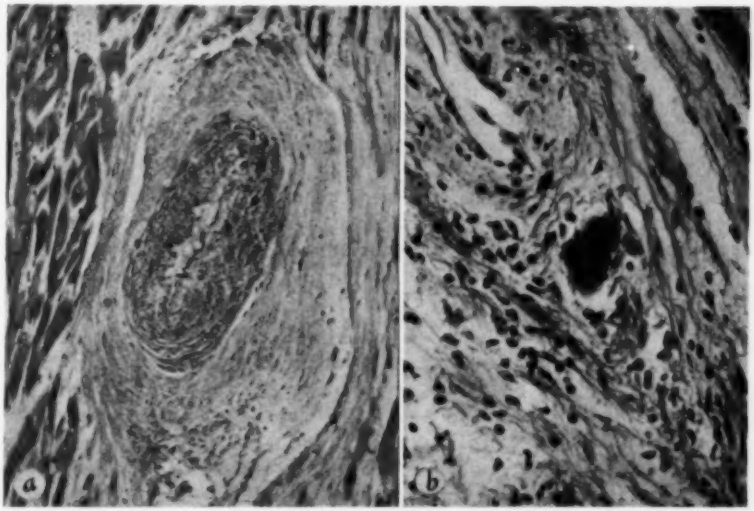

FIG. 4*a*. Myocardial perivascular fibrosis (hematoxylin and eosin × 130). *b*. Calcified embolus with granulomatous reaction (hematoxylin and eosin × 350).

Miliary infarcts were the most numerous lesion encountered, being present in 38 of the 43 untreated patients and in all nine of the treated series. For the entire series of 52 cases, they were found in 47 cases, or 90 per cent. Healing infarcts were the most commonly found type in the treated series, while acute infarcts were the most numerous type in the untreated series.

Nonspecific interstitial inflammatory lesions were found in 21 of the 43 untreated patients, being acute in 16, chronic in four, and showing abscess formation in one. In the treated series this type of lesion was present in five of the nine cases, being acute in one and chronic in four.

Perivascular lesions, inflammatory in nature, were present in 23 of the

untreated and in four of the nine treated patients. In the untreated series, acute perivascular lesions were found in 11 cases; abscess formation was found four times, and there was a chronic perivascular response in 14 cases. In one of the cases of the treated group the perivascular lesions were acute, and in the three other cases with perivascular lesions the lesions were chronic.

Aschoff nodules were found in only four of the 43 untreated patients and in one of the nine treated patients.

Emboli or thrombi were observed in 16 of the untreated and in four of the treated series. These were not always in immediate association with areas of infarction, though serial sections might have brought out this relationship more clearly. Angiitis was seen in four cases of the untreated series, but was not encountered in the treated series.

Perivascular fibrosis was found in 18 of the 43 untreated patients and in three of the treated series. It was impossible to determine the origin of the fibrosis, whether resulting from a healed Aschoff nodule, or from the end stage of a nonspecific perivascular inflammatory response.

The petechiae seen were in a case in which Dicumarol and a sulfonamide had been used.

In some instances lesions were very numerous, several being visible in one low-power field. In others, lesions were very infrequent, study of several sections revealing only one small area of involvement.

Comment

I. Bracht-Wächter Bodies. The term "Bracht-Wächter bodies" has been used to refer to the myocardial lesions in subacute bacterial endocarditis. As pointed out in the review of the literature, different authors have had varied opinions as to what constitutes the usual myocardial lesion. In our opinion, if the term is continued in use it should refer to the miliary infarct. Perhaps, because of the confusion, it would be better to discontinue its use, and to name the lesion instead as suggested by Saphir [11] and by de Navasquez.[12]

II. Frequency and Nature of Lesions. From our results in this series of cases, and from those of other investigators, it would appear that myocardial lesions could be found in a very high proportion of cases if one took sufficient sections from the myocardium. However, if the inflammatory lesions and infarcts are on an embolic basis, those cases in which the vegetations are confined to the right side of the heart should show no myocardial involvement. This was the case in our patient with the vegetations present on the tricuspid valve and on the mural endocardium of the right ventricle. Hamman and Rich [13] have also reported a case of subacute bacterial endocarditis in which the endocardial lesions were confined to the tricuspid and pulmonary valves, and in which the myocardium was essentially normal. The findings in these two cases suggest that bacteria or emboli, or the prod-

ucts thereof, must have direct access to the coronary circulation to produce myocardial lesions.

In relatively few cases in this series were there Aschoff nodules. In the series of others, Aschoff nodules were more common (table 1). Saphir and Wile [10] found a higher percentage of Aschoff nodules in children than in adults, and the fact that only one of our patients was less than 10 years of age may influence the statistics. In material from the Armed Forces Institute of Pathology, Saphir, Katz and Gore observed Aschoff bodies in only six of 76 cases of subacute bacterial endocarditis.

III. Effect of Myocardial Lesions on Myocardial Function. In the final analysis, one might ask whether the myocardial lesions are of importance in causing myocardial insufficiency or whether they are merely incidental findings. Thayer stated that myocarditis in subacute bacterial endocarditis was "not a very important lesion." Clawson [16] stated that

TABLE I

Aschoff Nodules in Cases of Subacute Bacterial Endocarditis

Author and Year	Patients	Aschoff Nodules (Patients)
Thalhimer and Rothschild, 1914[16]	14	1
Clawson, 1924[17]	54	6
Clawson and Bell, 1926[8]	61	7
Thayer, 1926[9]	23	1–2
Clawson, 1928[18]	60	27
Clawson, 1929[10]	60	36
Saphir and Wile, 1933[19]	10 (children)	10
Von Glahn and Pappenheimer, 1935[20]	26	12
Saphir, 1935[11]	35	14
Buchbinder and Saphir, 1939[21]	40	15
Saphir, 1946[13]	55 (adults) 15 (children)	19 11
Saphir, Katz and Gore, 1950[1]	76	6
This series	52	5

myocardial injury was a factor in cardiac failure in many cases of the disease. Buchbinder and Saphir concluded that lesions of the myocardium could adequately account for some cases of cardiac failure, but they could find no relationship between cardiac failure and demonstrable damage to the myocardium. De Navasquez was also unable to correlate the incidence of embolic foci with the degree of clinical cardiac failure, with the character and size of the vegetations or with the location of the valvular defect.

We were unable to find a significantly greater incidence of myocardial lesions in those patients who had had cardiac failure. Conversely, some of the persons who had had apparently good cardiac function terminally had quite extensive myocardial involvement. In some cases, however, lesions were so frequent that if the same held true throughout the myocardium there must have been a deleterious effect on function. Saphir, Katz and Gore demonstrated that the myocardial lesions could be associated with electrocardiographic abnormalities.

IV. Penicillin Treatment: Effect on Lesions. There was only one difference seen in the lesions of the treated as compared with the untreated series. That was the presence of the foreign body granuloma, similar to that described by Saphir.[13] The other lesions were present in approximately the same proportion in the treated as in the untreated series, except for the interstitial inflammatory lesions, which were predominantly acute in the untreated group and predominantly chronic in the treated group. One would expect to find the effects of small emboli from the vegetations, since they would continue to break off even after the vegetations had been sterilized. None of our treated patients had recovered from his infection for a sufficiently long period to bring about complete repair of the myocardial lesions.

Summary and Conclusions

Data on 43 nonpenicillin-treated and nine penicillin-treated patients who had subacute bacterial endocarditis were studied, particularly with reference to the microscopic appearance of the myocardium. Some type of myocardial lesion was found in all except the one case in which the endocarditis was confined to the right side of the heart. The most commonly encountered lesion was the miliary infarct. Other lesions included interstitial and perivascular cellular infiltrates or scars and emboli. Aschoff nodules were found in less than 10 per cent of the cases. A foreign body granuloma was present in one of the penicillin-treated series. Aside from this, the individual lesions in the untreated and treated groups were indistinguishable.

It is felt that myocardial damage is but one of the several factors operating to bring about myocardial failure in subacute bacterial endocarditis.

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SCREENING FOR CHEST PATHOLOGY USING MASS X-RAY SURVEY TECHNIC *

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Overholt and Atwell,[1] in discussing early cancer of the lung, state that there are no pathognomonic symptoms or group of symptoms, no characteristic physical signs and no typical progression of symptoms or signs. When symptoms do occur, they are typical of those produced by the common respiratory diseases. If the tumor has reached the point where it calls attention by the presence of symptoms such as persistent cough, chest discomfort, wheezing and hemoptysis, it is commonly incurable. The period when lung cancer is usually discoverable and curable is the so-called "silent phase." At this time the tumor has not yet caused symptoms but can cast an abnormal shadow on the x-ray screening film. It would appear that roentgen screening is at present the only way to speed up the detection of lung cancer.[2, 3] The facility with which this disease may be picked up by x-ray is indicated in the report of Ochsner, DeBakey and Dixon, who found that roentgenography yielded suggestive evidence of cancer in 85 per cent of their cases.[4] Since chest x-ray screening for tuberculosis has been in operation for many years, the modus operandi was already in existence. It remained to take advantage of the potentialities of the tuberculosis screening program to make it include chest tumors and other types of chest pathology. This involved no change in the basic program, but did mean a new approach in film interpretation and the addition of a follow-up program on patients exhibiting findings suspected of being other than tuberculosis. Whereas the finding of shadows not typical of tuberculosis had been of more or less academic interest, the labeling of these abnormalities as suspected tumors has now become a most important part of the reader's duty. As might be supposed, the suspicion rate of chest tumor will vary considerably depending upon what findings the film reader considers significant. In our study, the films were read by chest physicians and surgeons. Group conferences were held over films hard to interpret. Since cancer of the lung is principally a disease of the age group 45 and over, it was possible to keep the index of suspicion to a minimum by making available the age of the patient whose film was being read. This obviates unwarranted suspicion of findings in the younger age groups.

In a previous report [5] we described our findings for the study conducted from March to October, 1948, and also outlined our technic for obtaining follow-up information. Our present study includes 156,724 persons whose

* Received for publication January 3, 1951.

chests were x-rayed between April, 1949, and March, 1950. The group was a mixture of urban and rural population. The surveys were conducted in widely scattered areas in downstate Illinois and were all outside of Chicago.

Of the almost 157,000 films, 307 (or 0.2 per cent) had findings suggestive of neoplasm. There were 53,090 persons 45 years of age and over. From 307 follow-up questionnaires sent to physicians, 241 replies (78.5 per cent) were received. Seventy-six of the replies were of no value for study because 23 patients did not get in touch with the physicians named, 21 would not coöperate in further work-up, 15 were unknown to the physician named, and in 17 the diagnosis was deferred. There remained 165 replies of an informative nature, and their analysis is given in table 2. A further breakdown of miscellaneous pathology and nonmalignant neoplasms is given in tables 3 and 4, respectively.

TABLE I

Percentage of Deaths from Cancer of Bronchus, Lung and Pleura to All Cancer Deaths Occurring in Illinois, 1940–1948

Year	Total Cancer Deaths	Deaths from Cancer of Bronchus, Lung and Pleura	Per Cent of Total
1940	11,310	581	5.0
1941	11,590	675	5.8
1942	11,815	741	6.2
1943	12,142	788	6.4
1944	12,482	853	6.6
1945	12,865	914	7.1
1946	12,909	972	7.5
1947	13,446	1080	8.0
1948	13,682	1113	8.1

TABLE II

Analysis of Informative Replies to Cancer of the Lung Follow-Up Questionnaires

Chest essentially negative	57
Miscellaneous pathology	24
Nonmalignant neoplasms	10
Malignancies	14
Substernal thyroid	16
Tuberculosis	4
Healed tuberculosis	9
Cardiac	6
Bronchitis	5
Postpneumonic	4
Inflammation	4
Pleural thickening	3
Aneurysm	3
Hernia	2
Coin lesion	1
Bronchial adenoma	1
Asthma	1
Pulmonary fibrosis	1
Total	165

TABLE III

Miscellaneous Pathology by Type of Diagnosis

Pulmonary cysts	9
Malformation of chest	2
Eventration of diaphragm	1
Abnormality of diaphragm	1
Pneumoconiosis	1
Old rib resection	1
Calcified nodules	4
Enlarged aorta	1
Empyema	4
Total	24

TABLE IV

Nonmalignant Neoplasms by Type of Diagnosis

Benign tumors	3
Tuberculoma	4
Neurofibroma	2
Tumor of lung, type unknown	1
Total	10

TABLE V

Malignancies Found

Primary carcinoma
2 females, ages 34 and 53
8 males, ages 50, 57, 59, 61, 62, 64, 67 and 81

Metastatic carcinoma
1 female, age 56
2 males, ages 52 and 65

Lymphatic leukemia
1 male, age 73

In table 5 we have listed the actual cases of lung cancer reported to us. In comparing these with the cases reported during our first study, we find that there were 10 primary carcinomas out of 14 reported, whereas previously we found only three primary carcinomas out of 11 reported. Unfortunately, nine of the 10 primary lung cancers reported were well advanced. It is, of course, only the early primary case that can be treated successfully; with the exception of the occasional solitary metastatic lesion with no evidence of involvement elsewhere and with the site of origin satisfactorily treated.[6] Our case-finding potentiality would of course have been even greater, as indicated in table 7, if all of the questionnaires had been returned. Instead of 14 we could have found 25, or almost twice as many. In contrast to our first study, we found one case of primary carcinoma under 45 years of age. Table 8 shows that about 7 per cent of the deaths from lung cancer occur under the age of 45 years. On a percentage basis, the one case under 45 years represented about 7 per cent of the total number found.

Coincident with the last part of our study which was aimed at discovery of early primary carcinoma of the lung, we began our follow-up of cardiac suspects as determined from evidence of cardiac enlargement on the 70 mm. chest film. This included only those cardiac suspects referred to us by the Division of Tuberculosis Control. The period covered was January 1, 1950, to April 15, 1950. The number of persons x-rayed was 43,202; the number 45 years and over was 15,108. Questionnaires were sent on 217 suspects, and 92 informative replies were received. Of the replies, 16 gave no diagnosis, leaving 76 fully reported suspects. Table 9 lists the diagnoses made

TABLE VI

Deaths and Age Specific Death Rates for Bronchus, Lung and Pleura Cancer Occurring in Illinois, 1946–1948

Year	Age at Death							
	25 and Over		25–44		45–64		65 and Over	
	No.	Rate*	No.	Rate*	No.	Rate*	No.	Rate*
1946	965	19.6	58	2.4	587	31.3	320	49.7
1947	1075	20.8	77	3.0	642	32.7	356	52.5
1948	1109	21.1	72	2.8	654	33.2	383	56.2
Population Estimates Used								
1946	4,934,164		2,414,033		1,876,249		643,882	
1947	5,177,108		2,532,895		1,966,574		677,639	
1948	5,253,916		2,605,492		1,967,503		680,921	

* Per 100,000 estimated population.

TABLE VII

Cases and Age Specific Case Rates for Bronchus, Lung and Pleura Cancer Found by Using 70 mm. Chest X-Ray Survey: Illinois, April, 1949 to April, 1950

	Age		
	45 and Over	45–64	65 and Over
Persons surveyed	53,090	42,845	10,245
Suspects for neoplasm	222	144	78
Suspect rate per 100,000 persons surveyed	418.2	336.1	761.3
Malignant cases found (case rate*)	13 (24.5)	9 (21.0)	4 (39.0)
Number of fully reported replies received	118	75	43
Percentage of fully reported suspects found with neoplasm	11.0%	12.0%	9.3%
Maximal number of malignant cases which could have been found if all questionnaires had been fully reported** (case rate*)	24 (45.21)	17 (39.68)	7 (68.33)

* Rate per 100,000 persons surveyed.
** Method of computation—11.0% of 222 = 24.

TABLE VIII

Age Distribution of Mortality from Cancer of the Bronchus, Lung and Pleura Occurring in Illinois, 1948

International List Number (5th Revision)	Site	Age at Death					
		All Ages	Under 15	15–24	25–44	45–64	65 and Over
47 C, D, and E	Bronchus, lung and pleura	1113	1	3	72	654	383
47 C-	Bronchus	437	0	0	31	268	138
47 D	Lung	669	1	3	40	382	243
47 E	Pleura	7	0	0	1	4	2

for these 76 patients. The case rate for the fully reported suspects was 171.29 per 100,000 persons surveyed. If all questionnaires had been returned and properly filled out, the number of heart cases that could have been found would be 211, with a case rate of 488.4 per 100,000 persons surveyed. Table 10 gives some information other than the diagnosis as obtained from the 92 replies. Of the 10 cases in which the condition had not been previously known by the doctor, three were in the fourth decade of life, two in the fifth, two in the sixth and three in the seventh, or older. It is encouraging to note that 50 per cent of the unknown cases were found before the age of 60 years; the earlier a heart condition is known, the better the chance of setting up for the patient a régime that may prolong life and prevent disability. Also, a return of 10 per cent in unknowns having cardiac disease would appear to be worthwhile.

Screening devices have certain fundamental aims. They seek to discover disease early, so that the patient may be brought under treatment more promptly. This should lead to the prevention of certain chronic conditions, a decrease in complications, fewer cases needing long and costly care, greater rehabilitation and, of course, the saving of lives. Insofar as cancer of the lung is concerned, we aim at cure and rehabilitation. Anything short of this results in loss of life. In the case of heart disease, however, we are not

TABLE IX

Cardiac Diagnosis Obtained from Suspected Cardiac Follow-Up Questionnaires

Negative	2
Hypertensive heart disease	22
Rheumatic heart disease	18
Myocardial heart disease	17
Arteriosclerotic heart disease with hypertension	6
Miscellaneous heart disease	6
Arteriosclerotic heart disease without hypertension	3
Coronary heart disease	2
Total	76

aiming primarily at a cure but rather at prolonging life; at the same time we hope, through rehabilitation, to make it possible for the patient to lead as nearly normal a life as he can. We should therefore be as selective as possible, and screen only those groups from which we can expect the greatest return. To seek cancer of the lung under the age of 45 years is not practical; we should rather devote more effort to x-raying more people 45 years and over. Of the 74 fully reported cardiac suspects, 31 were 65 years of age and over. In this group were four of the 10 in which the condition was not previously known. It would seem that, if we are to set up a potentially beneficial régime for the cardiac, we should find him before he reaches the age of 65.

In x-ray screening of the chest, as in any screening procedure, the significance of the result will depend upon the number of people who submit to the procedure in question. It would seem that coöperation between the Tuberculosis Association, the Heart Association and the Cancer Society in a local chest x-ray survey would increase profitably the number of persons

TABLE X

Information Other than Diagnosis Obtained from Suspected Cardiac Follow-Up Questionnaires

Question Asked	Reply Made		
	Yes	No	Not Stated
Was the condition previously known?	73	10	9
Is the patient overweight?	39	46	7
Any evidence of hypertension?	46	37	9

x-rayed. Certainly such coöperative effort is justifiable. In any event, it is necessary that we increase by many thousands the number of people obtaining chest x-rays if there is to be significant accomplishment in a disease such as primary carcinoma of the lung.

Only early cases of bronchogenic carcinoma are amenable to treatment; therefore, it has been suggested that men over 45 have a chest survey every six months.[7] As pointed out by Boucot,[8] a chest survey is a screening process; therefore, the physician receiving a report of suspicious findings in one of his patients should make every effort to establish a diagnosis as rapidly as possible. Too many primary lung carcinomas do not receive early and adequate treatment because attempts are being made to establish the presence of the tubercle bacillus.

Another matter of importance relates to the value and significance of discovering certain types of chest lesions. For example, it would be helpful to know, of the conditions shown in table 2, which were of practical value to the patient's physician, and which were simply of academic interest. We should not attempt to justify a screening procedure merely on the basis of

finding something abnormal. Unless we were able to bring to the attention of the physician an unknown pathologic process needing and amenable to correction, our efforts would be ill-spent. We have already begun such a project.

Last, but certainly not least, we should call attention to the value of such a program from the point of view of professional education. The finding of each lung cancer suspect initiates a series of contacts with the patient's physician which will in most cases increase his diagnostic acuity. Among other things, as time goes by the physician confronted with the problem of a patient with suspected lung cancer will appreciate more keenly the need and value of consultation; also, he will know where and how to obtain such consultation. Comparing our two studies, we found that in the second series many more doctors took advantage of the consultation services of the State-aided cancer diagnostic clinics. It is felt that the program actually could be justified entirely on the basis of its educational value.

Summary

1. In a 70 mm. film chest x-ray survey of 156,724 people, 307 showed findings suggestive of chest malignancy.

2. Follow-up of these suspects led to the finding of 14 proved cases. Thirteen of the cases were in the age group 45 years and over.

3. Based on the reports received, 10 primary lung carcinomas were discovered. This is a considerable improvement over our previous study, in which only three such cases were found.

4. In a follow-up of 217 suspect cardiacs, as determined from 70 mm. chest x-rays in 43,202 persons, we found 74 cases of heart disease, as determined from 76 complete reports received in answer to our questionnaires.

5. In 10 per cent of the cases, the pathologic process discovered was previously unknown to the patient's physician.

6. Chest x-ray screening is the only hope at present of picking up early cases of primary lung cancer. It is necessary that we expand our coverage if we are to find enough of these cases to affect the death rate significantly. Our final potentiality in using this method of detection has not been settled, and we should continue follow-up studies until the question has been answered.

7. More consideration should be given to screening the most productive age groups, rather than all age groups.

8. The actual value of finding the many miscellaneous types of pathologic processes in chest surveys should be determined as nearly as possible.

9. Reports to physicians of evidences of cardiac enlargement appear to result in the discovery of a satisfactory number of unknown cardiovascular cases.

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SINUS BRADYCARDIA IN ACUTE RHEUMATIC FEVER *

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INTRODUCTION

SINUS tachycardia is widely recognized as one of the classic features of active rheumatic fever, but the fact that an abnormally slow heart rate is often present during the acute phase of this disease has received little emphasis.

Apparently the first report discussing the occurrence of sinus bradycardia in acute rheumatism was that of Andrieu and Aujalen [1] in 1936. Later, Keith [2] commented on the pulse rates observed in a large series of rheumatic children. He found that many cases developed a heart rate slower than normal as the acute phase of the illness subsided. Bradycardia was noted to occur more frequently in cases of moderate severity and in those patients experiencing their first attack of rheumatic fever. Keith found that the slow heart rate could be abolished by the injection of atropine, and he concluded that the mechanism at work was overactivity of the vagus nerve. Eden [3] has also reported the occurrence of transitory bradycardia during acute rheumatic carditis in children. In 1941 Glazebrook and Thomson [4] recorded pulse rates during the first four weeks of active rheumatism in 100 consecutive cases in boys 15 to 20 years of age. Thirty of their cases developed bradycardia. They noted that the slow heart rate usually appeared in the first week of the hospital course and lasted for from six to 13 days. The incidence of bradycardia was unrelated to the type of treatment or the severity of the attack. From their clinical impressions, Glazebrook and Thomson concluded that the occurrence of a slow heart rate in the acute stage of rheumatic fever indicated a grave prognosis, because of rapidly appearing permanent cardiac damage in many of the patients who manifested this sign. In 1946 Grossman and Graybiel [5] reported two cases of acute rheumatic fever in young adults with prominent sinus bradycardia early in the course of their illness.

During 1948 and 1949, 119 cases of acute rheumatic fever in young adult males were observed throughout the course of their disease at the Francis E. Warren Air Force Base Station Hospital in Cheyenne, Wyoming. The natural history of the illness in this group of patients was recorded.[6] The present report consists of an analysis of the occurrence and the significance of sinus bradycardia in this series of cases.

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Method of Study

The diagnosis of active rheumatic fever is at times established with difficulty, especially in that group of patients manifesting only a few of the signs of the disease following a streptococcal infection. In this study the criteria of Jones [7] were used as a guide in establishing a diagnosis. Migratory polyarthritis and demonstrable carditis were considered as major manifestations of the disease. Chorea and subcutaneous nodules, two findings commonly regarded as major signs of rheumatism, were of little import because of their rare occurrence in adults. Arthralgia, fever, erythema marginatum or multiforme, elevated erythrocyte sedimentation rate and suggestive electrocardiographic changes were listed as minor manifestations. The presence of a minimum of one major and two minor manifestations was required to establish a diagnosis of active rheumatic fever. Each case was considered individually, and various laboratory procedures were utilized freely to avoid erroneous diagnoses.

Daily electrocardiograms were recorded on each patient throughout the acute phase of the disease. The heart rates discussed in this report were obtained entirely from the electrocardiographic tracings. In the analysis, those cases in whom the electrocardiographic heart rate fell below 60 beats per minute during the first five weeks of the illness were classed in the bradycardia group. Only cases of bradycardia of sinus origin were included in this category; examples of a slow heart rate in association with heart block of any type were eliminated from the analysis.

Results

Of the original total, 106 cases were found to be satisfactory for inclusion in the analysis. Surprisingly, 59 (55 per cent) of these were found to have had electrocardiographic sinus bradycardia at some time during the first five weeks of hospitalization. Forty-seven of the patients had no such slowing of the heart rate.

The heart rate, temperature, erythrocyte sedimentation rate and various other clinical and laboratory features were recorded for each patient on summary charts. On examination of these it was apparent that a large number of cases exhibited a characteristic form of heart rate curve. This consisted of an early tachycardia during the febrile period, followed immediately by a phase of sinus bradycardia lasting from two to 14 days. The heart rate then returned to normal or elevated levels. Figure 1 is an example of a summarizing chart demonstrating the phase of bradycardia.

Though the time of appearance of the bradycardia in the hospital course was somewhat variable, it may be seen in table 1 that this sign most commonly became manifest during the second hospital week. Since the mean duration of fever and arthritis in this group of patients was one to two weeks,[6] it follows in a general sense that the slow heart rate usually became

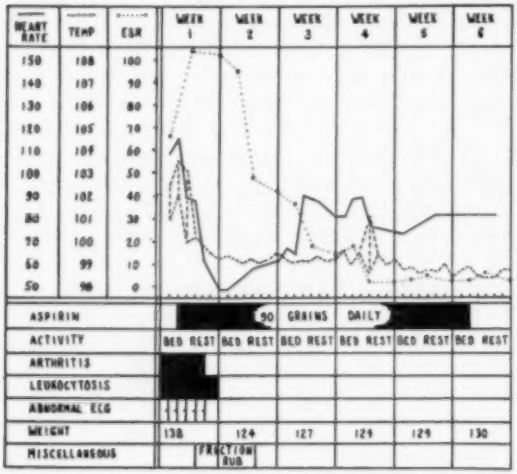

FIG. 1. Summary chart showing the first six weeks of hospitalization of a patient with acute rheumatic fever treated with aspirin. A period of sinus bradycardia is demonstrated early in the course of the illness.

evident during the subsidence of the acute phase of the illness. This correlation was observed repeatedly in individual cases.

It was of interest to attempt to determine if the bradycardia was related to the severity of the attack of rheumatism. Figure 2 presents graphically the relation of the slow heart rate to the height of fever and the duration of the acute arthritis. Though it was apparent that the relative percentage of patients developing bradycardia diminished somewhat as the severity of the attack increased, it was notable that cases of all degrees of severity were present in both groups. The data do not warrant the conclusion that the incidence of the slow heart rate is related to the severity of the rheumatic attack.

Keith [2] and Glazebrook and Thomson [4] reported that those persons suffering their first attack of acute rheumatic fever more commonly developed sinus bradycardia. In our series, 10 patients (17 per cent) among those

TABLE I

Period of Illness During Which Sinus Bradycardia Was Present

Hospital Week	Number of Cases with Bradycardia
1	9 (15%)
2	27 (46%)
3	12 (20%)
4	8 (14%)
5	3 (5%)

showing bradycardia and 10 cases (21 per cent) in the group with no slowing of the heart rate gave a past history of rheumatic fever. This would seem to indicate that the nature of the attack—that is, primary or recurrent —has little or no bearing upon the incidence of sinus bradycardia.

During the period of this study, the value of aspirin therapy was investigated in a controlled fashion. Of the patients included in this analysis, 60 received salicylate and 46 did not. Sixty-one per cent of the aspirin-treated cases developed sinus bradycardia early in the disease, while 49 per cent of the control cases who were given no salicylate manifested this sign. Since this difference is not statistically significant, aspirin therapy is probably unrelated to the development of sinus bradycardia.

The cases in this series were kept at bed-rest until all physical and laboratory findings had become normal and remained so for a period of two weeks. They were then gradually ambulated according to a constant plan. Figure

FIG. 2. This graph compares the severity of the attack of rheumatic fever in patients who did and who did not develop sinus bradycardia. The highest fever and the duration of the arthritis are used as indices of the severity of the illness.

3 is a comparison of the short-term prognosis in those patients who did and those who did not show sinus bradycardia during the first five weeks of their illness. As is seen in this graph, the development of a slow heart rate may be of some prognostic value in terms of duration of the immediate illness. Those patients who did not manifest this sign tended to suffer a more prolonged attack. Again, however, cases from the two classifications were found to have had both quite brief and very prolonged sieges, indicating that the prognostic reliability of this sign in an individual case is relative rather than absolute. In none of the cases in this series was there a fatal outcome. The ultimate prognosis in these patients is, of course, undetermined.

During their stay in the hospital (average period of hospital observation, six months), seven (11.8 per cent) of the cases in the group with brady-

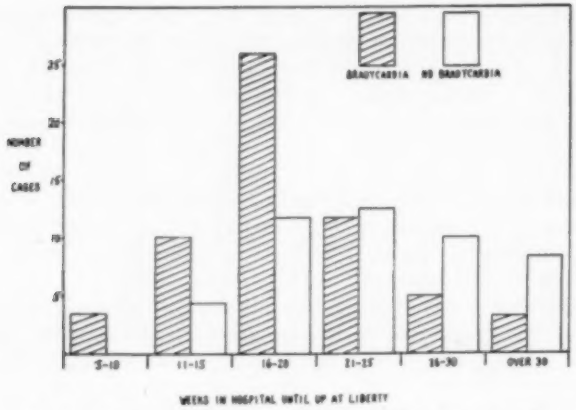

FIG. 3. This graph compares patients with and without sinus bradycardia in terms of duration of the attack of rheumatic fever. It is evident that those patients in whom a slow heart rate did not appear tended to suffer a more protracted illness.

cardia developed persistent heart murmurs considered to be of organic origin. Eleven (23.4 per cent) of the cases not showing bradycardia were found to have new murmurs of similar character. Since this difference could occur by chance 15 times in 100, it is only suggestive and statistically not of sufficient significance to justify any conclusion. Again, more prolonged observation would have yielded more satisfactory information on this point.

DISCUSSION

The mechanism responsible for the production of this slow heart rate in the course of active rheumatic fever is obscure. Most writers have ascribed it to vagal overactivity.[2, 4] It is possible that bradycardia might be produced by inflammation about the sinoauricular node and may have, in some regards, the same significance as a prolonged P–R interval.[5] In the present work, it was noted that the period of bradycardia was correlated with only one factor, namely, the subsidence of fever and arthritis. This suggests a possible "physiologic" mechanism for the bradycardia. It is well recognized that a slow heart rate commonly appears following fall in fever in certain illnesses, such as scarlet fever. Perhaps this same phenomenon occurs in acute rheumatic fever, provided the degree or location of carditis is not such as to produce a persistently rapid heart rate.

It should be emphasized that the findings here reported are concerned only with rheumatic fever in the young adult white male. Since this disease in other race, sex and age groups has a different natural history, the observations and conclusions may not be summarily applied to all cases of rheumatic fever.

Summary

In the young adult white male afflicted with acute rheumatic fever, sinus bradycardia frequently develops during the first few weeks of the illness. The appearance of the slow heart rate is correlated in time with the subsidence of fever and arthritis. The incidence of this bradycardia is not related to a past history of rheumatism, to the severity of the attack or to the use of aspirin in treatment. Those patients who manifest this period of bradycardia have a somewhat more favorable short-term prognosis in relation to the duration of the immediate illness, and they may possibly have a more favorable ultimate prognosis in terms of residual cardiac damage. Possible mechanisms producing the bradycardia are discussed.

Acknowledgment

The authors wish to express appreciation for the assistance of John K. Cullen, Colonel, Medical Corps, United States Air Force, and Irvin Chamovitz, formerly Captain, Medical Corps, United States Air Force, without whose help this work would not have been possible.

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OLD AGE IN THE BIBLE AND POETRY *

By Louis A. M. Krause, M.D., F.A.C.P., *Baltimore, Maryland*

The finest description of old age, describing its organic changes in classical prose, is found in the Book of Ecclesiastes, written about 400 years more or less before the days of Christ. Let us consider each verse separately, looking at it through medical eyes.

"Remember now thy creator in the days of thy youth
While the evil days come not nor the years draw nigh when thou shalt say I have no pleasure in them."

Here obviously the speaker is talking to young people, saying "remember thy creator in the days of thy youth." This we must always emphasize to young folks because it isn't difficult to have older people thinking about their God. He adds "while the evil days come not, nor the years draw nigh, when thou shalt say I have no pleasure in them." It is rare for us to hear young people talk about having no interest in living, that they are willing to pass on if the Lord should call them; but how frequently do we hear that from old people? Many times I have heard them say, "When the Lord calls me, I'm willing to go, I've lived a long life and had a happy life, and reared a family," and so on. However, this should never be heard from a young person. The next verse:

"While the sun, or the light, or the moon, or the stars be not darkened nor the clouds return after to the rain."

Here is more beautiful imagery. Let something happen in the young person's life. It is comparable to a thunderstorm in the summertime. Dark clouds, lightning, thunder, torrential rain! Yet within a few hours the clouds part, the sky is blue again. But let something happen in the old man's life. Let him lose his savings or his job. Can he go out and recapture them? You know the answer as well as I, he cannot. And how does the author express it here in this Book of Ecclesiastes? "the clouds return after the rain." Beautiful imagery. The next verse:

"In the day when the keepers of the house shall tremble, and the strong men shall bow themselves."

In the "keepers of the house," here he becomes very personal, talking about the body as a house in which the soul dwells. That's a concept that has been used by many people over generations and ages. It is used in the New Testament as well as the Old. If my body is that house, the keepers of my body obviously are the hands. They wash me, feed me, earn my

*Delivered under the title, "A Biblical Introduction to Geriatric Medicine," at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 13, 1951.

living, and so on. And when do we notice shaking of the hands? Those of you in medicine will immediately recognize it as the arteriosclerotic tremor or the shaking that we see in paralysis agitans, the so-called shaking palsy. Notice the writing of an old man and compare it with his writing when he was young. You will note a great difference. In the next sentence "the strong men shall bow themselves." If my body is the house that is referred to, a body needs a foundation as well as this building in which we are meeting. The foundations of this body are the legs and the hips and the thigh. They support us, but when do they bow? One needs only to watch the gait and stature of the old man. Notice the bowing of the legs and the tilting forward that we see in his gait. Then he gives the whole thing away in the next sentence when he says, "And the grinders cease because they are few." The grinders obviously are the teeth as you have already guessed. When do your teeth fall out? Well, you know the answer as well as I do. You see, everything fits in so well with this picture of aging. Then he adds, "Those that look out of the windows be darkened." He could have used another term here, the Hebrew has a perfectly good word for eyes, but the Oriental writers are always prone to use flowery imagery whenever they can. When he speaks here, "Those that look out of the window," if my body is the house, the windows of my body obviously are the eyes. When do they grow dim, when do we have to hold things farther and farther away, when do we get presbyopia, when do cataracts come on? You know the answer, as one grows older. Then in the next verse, "The doors shall be shut in the streets." If my body is the house, the sound can only come into my body by way of my ears, and in the Hebrew here we could use the term two doors rather than the word doors. The two doors shall be shut in the streets, and that refers clearly to hearing; when do we cup our ears? The next time you go to any big meeting, notice the audience, see who cups ears, always, or rather frequently, the older folks. He adds also the same cue that he gave us in the verse above, "When the sound of the grinding is low," referring to the fact that the teeth are gone. Continuing he adds, "He shall rise up at the voice of the bird." Who gets up early in your house, the older folks or the youngsters? You know that it is the older folks who are more commonly up early in the mornings. They have gotten the fire started, coffee made. The young people we can hardly drag out of bed in the morning. Then he adds, "And all the daughters of music shall be brought low." Again we have more Oriental imagery. This can only refer to the nightclubs, the dancing girls. That's the term for nightclubs that is frequently used in many other languages, the daughters of music. You know as well as I how many of the nightclubs here in this city are crowded with 70 and 80 year old people! The daughters of music are brought low, signifying the loss of interest in such pursuit as one grows older. Also, "when they shall be afraid of that which is high"—it is clear that he refers to the old

people who are careful, uncertain about their gait and very timid about going on elevated places and ladders. "Fear shall be in the way." They have that uncertainty in their position, and gait, and station. Notice the next time you take an airplane trip how many people of the older age group are in the plane with you. More frequently it is the youngsters, rarely the older people because fear is in their way, and don't forget it works the other way too. That without those fears, you may not get to be an old person. The next line reads, "The almond tree shall flourish." There, you'd have to know what an almond tree looks like when in bloom. The almond blossoms close at hand appear a faint pink, but at a distance they appear white. Here because of the context and because this imagery has been used in other literature, it must refer to the gray hair, "the almond tree shall flourish." Then we come to another difficult passage, "The grasshopper shall be a burden." Because of the term and the word, grasshopper, and the context "the desire shall fail," we certainly are justified in assuming that this refers to the sex ability and to the waning of that ability as one grows older. Here it can only mean that because he further adds, "and the grasshopper shall be a burden," and "desire shall fail." Finally "because man goeth to his long home," man goes to his long home, his heavenly home. "And the mourners go about the streets." The mourners in the Orient follow the funeral about a square or two in the rear and they wail and toss their veils and hair about. These are the paid mourners that we are familiar with in the Orient. Next, "or ever the silver cord be loosed" we must suspend our judgment here because it is not too clear what may have been meant. If one follows the various mythologies of the Orient, one may conclude it probably refers to the spinal cord. The silver cord may refer to one's coördination, one's station and gait and position, although it is difficult to say exactly, but the context may justify such an assumption. "Or the golden bowl be broken." Our imagery may suggest several things. It is interesting that nowhere in the Old or New Testaments do we have a reference to the brain as having a specific function. They were well aware of the brain. They had seen it in skulls bashed open in battle and in animals. But it may refer to other organs, the liver or kidney, who knows, because they frequently placed the emotions or the thought processes in the kidneys and the liver. In either event, whether it is the brain or the heart or any other organs, "or the golden bowl be broken," whether it is apoplexy of the brain with a stroke or apoplexy in the heart with coronary thrombosis, it does signify a serious complication. "Or the pitcher be broken at the fountain or the wheel broken at the cistern." Here the interpretation is more certain. Obviously it refers to an organ of excretion, probably excretion of water, "The pitcher be broken at the fountain," the fountain where water is produced, comparable to the function of the kidneys, producing water. You know that is our problem in medicine,

when we see the old patient, we are constantly worried about his kidneys. That's our worry about the old man and the old woman, as to whether the kidneys will be able to withstand the illness or the operation, as the case may be. And then He adds, "Or the wheel broken at the cistern." Here we again picture the imagery of cistern where water is collected, not where it is produced, and that is our problem in the old man or the woman when bladder function is in difficulty, the man having retention, difficulty in voiding; and the old woman difficulty of retaining, where there is constant incompetence, stress incontinence particularly. So then he closes with, "Then shall the dust return to the earth as it was; and the spirit shall return unto God who gave it."

Thus concludes one of the finest medical literary gems I know, written by a very keen observer probably a Sadducee living in Jerusalem. It is to be regretted that he did not express himself on the psychology of old age, but confined himself only to the organic changes.

In concluding, I know of no better description of the psychology of old age than the poem written by Dr. Oliver Wendell Holmes called "The Last Leaf." This poem should be really added to that remarkable chapter of old age in the Book of Ecclesiastes. It concerns an old neighbor, Major Thomas Melville, grandfather of Herman Melville, who frequently passed the poet's door, on his morning walks. It goes as follows:

And I saw him once before,
As he passed by the door
and again
The pavement stones resound
As he totters o'er the ground
With his cane.
They say that in his prime,
E're the pruning knife of time
cut him down,
Not a better man was found
By the crier on his round
Through the town.
But now he walks the streets
And he looks at all he meets
Sad and wan,
And he shakes his feeble head,
That it seems as if he said,
"They are gone."

Here we have a sad picture of an individual with no living bond with the living. His loved ones and his friends have all passed on. He seems not to belong to those living about him. In the next stanza we really reach the depths of pathos in old age and those who survive their loved ones. It goes as follows:

The mossy marbles rest (tombstones of graves of his loved ones and friends.)
On the lips that he has prest (The lips of loved ones that he kissed when they were living)
In their bloom,
And the names he loved to hear
Have been carved for many a year
On the tomb. (All his loved ones and friends are gone. He alone survives but has no living bond with the living.)

Continuing the poet states,

My grandmama has said
Poor old lady, she is dead
Long ago
That he had a Roman nose,
And his cheek was like a rose
In the snow.
But now his nose is thin
And it rests upon his chin
Like a staff. (His teeth are gone, you notice.)
And a crook is in his back
And a melancholy crack
In his laugh.

I know it is a sin
For me to sit and grin
At him here
But the old three cornered hat,
And the breeches, and all that, (Notice how old folks stick to their old fashions.)
Are so queer.

Finally regardless of how old we get to be, if we are in our right mind, we still cling to life. The poet winds up in a jubilant note expressing such a thought:

And if I should live to be
The last leaf upon the tree
In the Spring,
Let them smile as I do now
At the old forsaken bough
Where I cling.

To paraphrase Edmund Spenser: Here then is a likelihood of truth as a result of conferring of time, language and the like. I did hunt out a probability of things which I leave to your judgment to believe or refuse.

CASE REPORTS

AN UNUSUAL CASE OF PHEOCHROMOCYTOMA WITH FATAL OUTCOME *

By Norman O. Rothermich, M.D., F.A.C.P., *Columbus, Ohio*

The syndrome of paroxysmal hypertension associated with tumors of the chromaffin tissue, usually of the adrenal medulla, has become well known, and the clinical recognition and successful surgical removal of these tumors are being achieved with increasing frequency in recent years. These tumors are almost always anatomically benign but, because they produce such profound effects on the patient's physiology, they have a stirring and dramatic appeal, and the current literature is filled with case reports emphasizing one or another special or unusual feature. Individuals harboring an active pheochromocytoma are always in imminent danger of sudden death, and hence, regardless of the microscopic appearance, these tumors must be considered clinically malignant.

Although these tumors were first described in the latter part of the Nineteenth Century, their clinical significance was not fully appreciated until about 25 years ago, and the first report of the correct preoperative diagnosis and successful surgical removal with subsequent clinical cure was apparently that of Pincoffs [1] in 1929. A thorough and exhaustive treatise on the subject was prepared by MacKeith [2] in 1943. In 1945 the not inconsiderable problem of making a clinical diagnosis was greatly facilitated by the discovery of Roth and Kvale [3] that histamine exerts a very specific provocative effect in such patients. Since that time excellent reviews of the subject have appeared in the literature,[4, 5] but in no case was there mention that the clinical diagnosis had ever been made except where an elevation of the blood pressure had been recorded. The following case report is believed to contain several features which are unusual and of sufficient interest to warrant publication.

Case Report

The patient, a 25 year old white female, was admitted to University Hospital at 7 p.m. on March 29, 1948, apparently in a dying state.

According to the patient's husband, the present illness had begun two days previously with sudden onset of fullness in the head, intense throbbing headache, palpitation and pounding of the heart, coldness of the extremities, extreme nervousness and tremulousness. The patient perspired profusely, and when the attack subsided after an hour or so she was exhausted. However, in a short while she began to feel better again and continued with her routine household duties. Similar attacks recurred at intervals throughout that day, but the patient had a fairly good night's sleep and awoke the following morning feeling well. About noontime the symptoms returned rather abruptly, and throughout the remainder of the day they continued with frequent

* Received for publication March 11, 1950.
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but shorter periods of remission. Early in the morning of the day of hospital admission the patient was awakened with a similar attack; however, this lasted only about a half-hour and the patient was able to drop back to sleep. When she again awakened she felt well enough that her husband decided he could go on to work. The patient was four months pregnant at the time and was scheduled for a prenatal check-up with her obstetrician that afternoon. About 1 p.m. the patient called her husband on the telephone and stated that she had been having severe attacks of the same symptoms almost continuously all morning and that she was beginning to feel quite ill.

The husband returned home to find his wife completely prostrate, gasping for breath and somewhat blue around the lips. The obstetrician was called to the house and found the patient in critical condition, with marked dyspnea, orthopnea and cyanosis. The blood pressure was unobtainable and the heart action very rapid and feeble. Medical consultation was then sought and the patient was sent into the hospital.

The husband volunteered that both he and his wife had tended to ignore the onset of this present illness, since the patient had had so many similar attacks in the preceding five or six years that she had "sort of gotten used to them." Besides, they had gone to physicians on numerous occasions seeking relief or an explanation for her episodic symptoms, and each time an examination revealed nothing abnormal and the patient was advised that the symptoms were due to her nerves. Since his wife tended to be of phlegmatic and stoical disposition, the husband felt quite sure that many such "nervous attacks" went by without mention or complaint from the patient. Often, however, the husband knew from the ashen-gray color of her face and tremor of her hands that the patient was not well. Also, during these spells, the husband could observe an actual vibration of the head, seemingly synchronous with the heart beat, and the entire precordium could be seen to heave with each heart beat. Between episodes the patient enjoyed excellent health and seemed carefree and unworried by any personal or marital problems. She found it comparatively easy to care for her two children and manage her household duties and was having no trouble with her present pregnancy. She had made regular prenatal visits during all her pregnancies and apparently had had her blood pressure checked each time, but this had always been found normal.

Past History: The patient had always enjoyed good health, with no known illnesses except childhood diseases, until five years prior to her present illness. At that time she had developed a nodular goiter and had had a thyroidectomy performed. Her postoperative course was uneventful and she was discharged from the hospital in 10 days. The hospital record was reviewed and two things seemed worthy of note. Under the heading of past history it was stated that "when she exercises, she has a sensation of blood rushing to her head, her hands shake and she itches under the arms." The other notation was the microscopic report of the surgical specimen of thyroid tissue: "an adenocarcinoma with metastasis to regional lymph nodes." It was stated that the patient received a course of roentgen-ray therapy to the entire neck region.

In the four years preceding the present illness the patient had gone through two pregnancies more or less uneventfully and had delivered a normal baby in each case. The husband stated very positively that during both of these pregnancies the patient had continued to have her usual spells of nervousness, headache and palpitation, but he was equally certain that these had never occurred under a doctor's observation. A review of the hospital records of each pregnancy disclosed normal blood pressure records, except for one of 140 mm. Hg systolic and 90 mm. diastolic, taken sometime during labor. The patient's past medical history and family history were otherwise not remarkable.

Physical Examination: At the time of admission the patient, a well developed and well nourished young white female, was moribund, oblivious of her environment and in a state of shock. Rectal temperature was 101°. The pulse and blood pressure could not be obtained. Respirations were rapid and shallow, productive of loud rattling and a frothy red fluid which exuded from her nose and mouth. The loud respiratory rattling completely obscured all heart tones and peripheral lung sounds. The abdomen showed a hypogastric mass consistent with a four months pregnancy. It was not otherwise definable or remarkable. Neurologic examination was negative. The pupils were widely dilated, and the ocular fundi showed no pathologic changes. The deep tendon reflexes were markedly depressed but equal. No pathologic toe signs could be elicited.

Emergency therapeutic measures were instituted and within an hour the patient had shown definite improvement, with some clearing of the lung fields and less dyspnea. The heart tones were at least audible, and a rate of 150 could be counted. The patient was more alert, and complained of excruciating substernal oppression which required morphine.

By this time an electrocardiographic tracing was available and revealed ventricular paroxysmal tachycardia (figure 1).

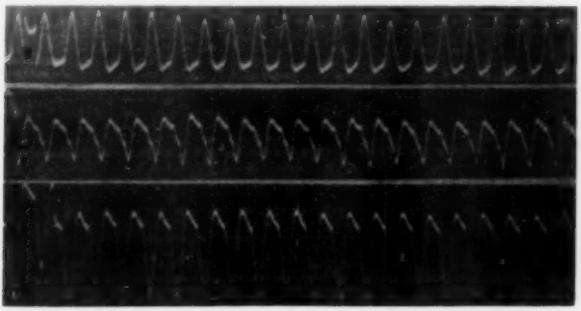

FIG. 1. Electrocardiogram at the time of admission, showing ventricular tachycardia.

Laboratory studies showed the following: The erythrocyte count was 5,250,000, hemoglobin 15.8 gm., leukocyte count 32,500; differential count, 42 per cent nonsegmented leukocytes, 45 per cent segmented leukocytes, 13 per cent lymphocytes. Urinalysis showed a specific gravity of 1.017 and 375 mg. per cent albumin; it was negative for sugar, acetone and diacetic acid; the microscopic examination was negative. The blood urea nitrogen was 20 mg. per cent. A repeat blood count the following day gave almost identical findings. Repeat urinalysis the following morning on a catheterized specimen gave entirely normal findings with negative albumin.

Therapy was directed primarily at the ventricular tachycardia: quinidine, gr. 10, was administered per rectum in five pin-punctured capsules each containing 2 gr. Thereafter, quinidine could be given by mouth and was administered in doses of 6 gr. every hour. A total of approximately 76 gr. of quinidine was given without appreciable effect on the ventricular tachycardia, although electrocardiographic tracings were taken hourly. One tracing, taken after the patient had received about 55 gr., was variously interpreted as ventricular fibrillation or a break-through of sinus rhythm with frequent ventricular extrasytoles (figure 2). The fact that the patient

lived for 12 hours after that tracing was taken speaks against the interpretation of ventricular fibrillation.

About 23 hours after hospital admission the patient seemed to be doing moderately well, although still in critical condition with a heart rate above 160 and rapid respirations. The cyanosis had cleared slightly, and the patient was aware of her environment and able to talk, when she suddenly gasped for air and died shortly afterwards. Clinical diagnoses: (1) pheochromocytoma; (2) possible coronary occlusion with myocardial infarction, and (3) pregnancy, four months.

Extract from the Autopsy Protocol: The heart weighed 320 gm. The epicardium was normal. Valve measurements were normal. The myocardium of the left ventricle measured 22 mm., that of the right ventricle 6 mm. The myocardium was somewhat soft but not otherwise unusual.

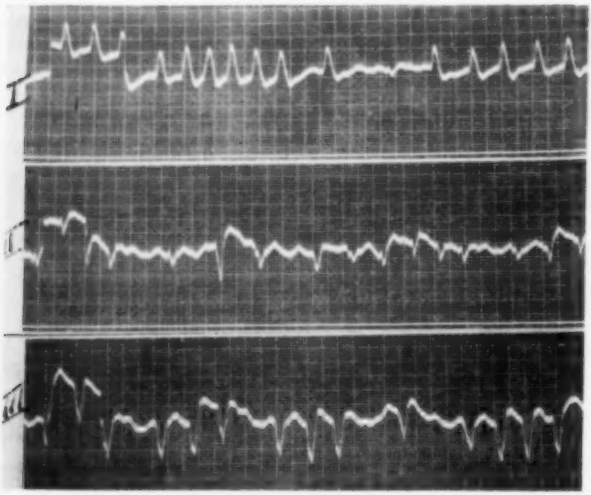

FIG. 2. Electrocardiogram after quinidine therapy: Lead I shows ventricular tachycardia with long pause and a supraventricular beat; Lead II shows bursts of sinus rhythm; Lead III shows return of tachycardia with pauses.

The lungs showed congestion and edema but no evidence of pneumonia. The spleen weighed 200 gm. and was normal in all respects. The liver weighed 1,200 gm. and it too was normal in appearance. The gall-bladder, pancreas and gastrointestinal tract showed no noteworthy abnormalities.

The right adrenal gland was identified by the large mass separating it from the right kidney. On close examination the cortex of the right adrenal was seen to be intimately associated with the mass. The mass measured 8.5 cm. in diameter and appeared to be well encapsulated. Surrounding the capsule was a recent hematoma. The mass was sectioned and found to contain soft hemorrhagic brownish tissue. The right adrenal and attached tumor weighed 450 gm.

The left adrenal weighed 25 gm. and, on section, a 1 cm. gray nodule was found in the medulla. This was thought to represent an adenoma or hyperplasia of the left adrenal medulla.

The kidneys and bladder were normal in appearance. The uterus contained a four month old fetus weighing about 300 gm. Thyroid was absent.

Microscopic sections showed the lungs to contain severe congestion and edema consistent with acute left heart failure. Both the large tumor in the right adrenal and the small tumor in the left adrenal showed all the typical appearances of a pheochromocytoma (figure 3). Sections of the heart muscle showed a diffuse interstitial inflammation, with numerous eosinophils consistent with a diagnosis of acute isolated or Fiedler's myocarditis (figure 4).

The final pathologic diagnosis was: (1) pheochromocytoma, adrenals, bilateral; (2) myocarditis, acute isolated, with cardiac dilatation; (3) congestion and edema, pulmonary, and (4) pregnancy, four months.

Discussion

So far as is known, a clinical diagnosis of pheochromocytoma has not been made without a recording of hypertension at some time in the patient's lifetime and without the aid of any of the diagnostic laboratory tests. In this case, the patient's condition at the time of her hospital admission was so grave that little thought was given to differential diagnosis. Nevertheless, it was felt that in an apparently healthy young woman who had not been on digitalis and in whom there was no antecedent history of any type of heart disease, ventricular tachycardia was indeed an extremely rare occurrence. When this finding was coupled with the classic history obtained from the husband and the obvious signs of severe left heart failure, pheochromocytoma seemed the only logical diagnosis.

Supraventricular paroxysmal tachycardia was considered as a possibility, but this rarely produces severe headache, sweating, or blanching or coldness of the extremities; each episode almost invariably has an abrupt termination, and its rapid progression into ventricular tachycardia and left heart failure in a young woman who had had attacks for only a few years seemed extremely unlikely. Essential hypertension with crises was ruled out by the absence of any blood pressure elevation. Thyrotoxicosis with crisis might produce such a terminal picture but is hardly likely to give rise to such isolated attacks. Although the patient had been having symptoms throughout the two days preceding hospitalization, these symptoms were coming in paroxysms and between episodes she felt fairly comfortable. Other conditions which may produce paroxysmal hypertension, or which may give rise to a similar history, include the following: eclampsia, lead poisoning, tabes dorsalis, angina pectoris, affections of the vagus, thalamic tumor, periarteritis nodosa, migraine, cardiac neurosis, anxiety state, and even the hypertensive diencephalic syndrome (MacKeith). However, all of these could be ruled out fairly definitely for one reason or another. For the most part, the fact that paroxysms had been present for four to five years, with healthy asymptomatic intervals, would exclude any of the chronic diseases or the diseases which terminate fatally in a shorter time. The others, such as cardiac neurosis, are not likely to eventuate in ventricular tachycardia with severe left heart failure and death.

The most common mode of death in pheochromocytoma is said to be from acute pulmonary edema, circulatory collapse and cerebral hemorrhage (MacKeith). Death with high fever is described, and five cases died suddenly and unexpectedly in the hospital while undergoing investigation or awaiting operation

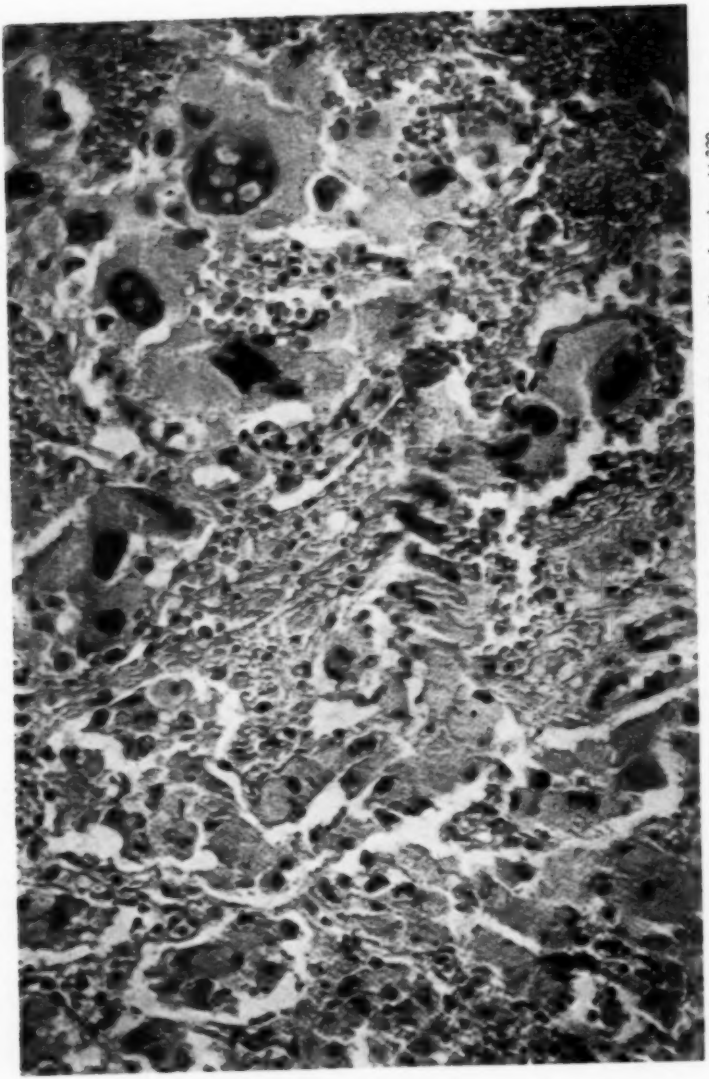

FIG. 3. Photomicrograph of pheochromocytoma of right adrenal. Hematoxylin and eosin. × 320.

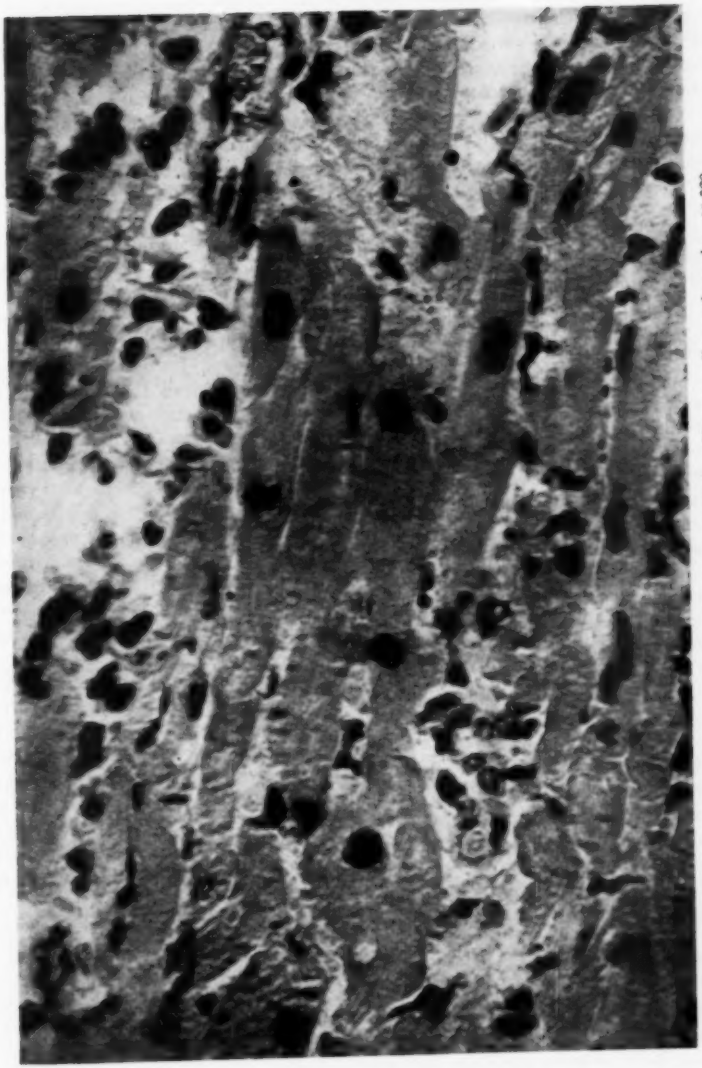

FIG. 4. Photomicrograph of isolated myocarditis. Hematoxylin and eosin: ×320.

(MacKeith). Runs of ventricular tachycardia have been reported (Pincoffs), but this is the first case in which such an arrhythmia was a fatal complication. As soon as the ventricular tachycardia was discovered, quinidine therapy was instituted and a total of 75 gr. administered in a period of 18 hours, but it was ineffective in influencing the abnormal rhythm. After the administration of 54 gr. of quinidine, an electrocardiographic tracing suggested a return to sinus rhythm with frequent ventricular extrasystoles. On the basis of this the quinidine was withheld for three hours. When a tracing then showed a return of the tachycardia, quinidine therapy was resumed but was without effect.

The most unexpected feature in this case was the histopathologic diagnosis of acute isolated myocarditis. Dr. Eleanor Humphreys,[6] of the University of Chicago, states that she had reviewed the world literature to date on cases of pheochromocytoma coming to autopsy and that in no case had there been any report of this complication. In most cases there was either inadequate mention or none at all of the microscopic appearance of the heart.

Whether the myocarditis was caused by or had any etiologic relation to the pheochromocytoma, or appeared as a coincidental and unrelated condition, is of course unknown. However, a search of the literature suggests that it would not be too unreasonable to expect such a complication in conjunction with an adrenalin-producing tumor. Saphir,[7] in his comprehensive review of the subject of acute isolated myocarditis, quotes the work of Hansmann and Schenken [8] in which they produced acute isolated myocarditis in experimental animals with various substances and in which the best results were uniformly obtained with epinephrine combined with sparteine. Mention may also be made of the report of Franz [9] on the autopsy findings of a patient who for many years had been treated with epinephrine because of bronchial asthma. Franz stressed that the fibers of the heart muscle were apparently primarily damaged, perhaps as a result of administration of epinephrine or possibly because of a definite hypersensitivity to the substance.

It is stated by Goldzieher [10] that a single dose of adrenalin may cause myocardial changes, especially if caffeine is added. Raab [11] has demonstrated experimentally that sympathomimetic amines are exquisitely vasocardiotoxic drugs, and in two subsequent papers [12, 13] he reports the finding of excessive concentration of epinephrine-like substances in the myocardium of two patients who were apparently healthy and died suddenly without apparent cause. One patient had a thyroiditis, however, and Raab states later in the paper that, in rats, doses of epinephrine usually innocuous proved rapidly fatal if the animals were given thyroxin previously. In our patient there was complete absence of thyroid tissue as a result of operative removal five years before. She had been taking thyroid therapy, but no definite information could be obtained as to the dosage or the possibility that she had taken an excessive amount shortly before her death.

From the comprehensive review of Saphir on the subject of acute isolated myocarditis, one might assume that the theory of infectious etiology in that condition had been largely discarded, and that the condition represented a hypersensitivity to one or many different kinds of drugs or chemicals. Unfortunately, in the case reported here, cultures were not obtained from the myocardium, but, as Saphir indicates, it is extremely doubtful that they would have yielded any pathologic growths. The leukocytosis of 30,000 or more is a common finding in acute isolated myocarditis, and the very brief duration and singularity of the pathologic

findings would make it unlikely that a bacterial or virus infective agent could be responsible for the pathologic lesions in the heart muscle.

If it can be assumed that the hyperadrenalinemia produced by the pheochromocytoma caused the acute isolated myocarditis with ventricular tachycardia and death, then this case is a clinical demonstration of active inflammatory disease arising from a qualitatively normal, though quantitatively abnormal, physiologic mechanism. In other words, an intermediate physiologic mechanism for expression of the alarm reaction became itself pathologic by virtue of tumor formation, and a disease of adaptation (Selye [14]) was produced by an intrinsic derangement of the adaptive mechanism without shock and countershock phases or external environmental noxae.

Summary

A case of bilateral adrenal pheochromocytomas in a 25 year old pregnant patient is reported. The clinical diagnosis was made on the basis of the history, the ventricular tachycardia and evidence of left heart failure, without benefit of the finding of an elevated blood pressure. The autopsy showed, in addition, acute isolated myocarditis (Fiedler). The causal relationship between pheochromocytoma and acute isolated myocarditis is discussed.

Acknowledgment

A pathologic report and opinion were supplied by Dr. Emmerich Von Haam, to whom I am also grateful for valuable aid in the preparation of this manuscript.

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A CASE OF FATAL BILE PERITONITIS FOLLOWING LIVER NEEDLE BIOPSY *

By Albert I. Rubenstone, M.D., Solomon S. Mintz, M.D., and David R. Meranze, M.D., *Philadelphia, Pennsylvania*

It is the purpose of this paper to present a case of fulminating bile peritonitis and death following liver needle biopsy and to point out the hazard of this procedure in cases of obstructive jaundice.

No case of death due to bile peritonitis following liver needle biopsy has as yet been reported. Several authors list this danger as a theoretical possibility (Roholm, Krarup and Iversen,[1] Hoffbauer [2]). The former believe that in two instances of liver needle biopsy they aspirated pure bile from either a large dilated bile duct or from the gall-bladder. Since the first use of liver needle biopsy by Lucatello [3] in 1895, 14 deaths from complications have been reported in the literature, 12 thoroughly reviewed by Hoffbauer [2] in 1947, and two reported by Klofer [4] in 1940. All of the fatalities except two resulted from hemorrhage. In the latter two, the deaths could not be unequivocally attributed to the procedure. Several non-fatal cases with clinical signs and symptoms of localized peritonitis following liver needle biopsy have been described in the literature.

Case Report

A 57 year old white housewife was admitted on October 11, 1948, with malaise, chills and weakness. She had been hospitalized three months previously for a period of 31 days with fever of undetermined etiology. On this second admission the patient was grossly jaundiced. Pruritus had developed nine days before admission. Her stools had been light-colored for three weeks. Physical examination revealed moderate jaundice, a liver palpable two fingerbreadths below the right costal margin, and a palpable spleen. The blood count, urinalysis and blood urea nitrogen values were within normal limits. Blood sugar was 134 mg. per cent. The patient was placed on high protein, high carbohydrate diet with a supplement of vitamins. The results of a battery of liver function studies, performed on several occasions, were indecisive in the differential diagnosis between medical and surgical jaundice, and a liver biopsy for diagnostic purposes was done on October 28. A standard Vim Silvermann needle was used. The approach was intercostal. The liver was percussed and a point in the second intercostal space below the cephalad level of liver dullness and in the anterior axillary line was selected as the site of entrance. The biopsy was obtained under aseptic surgical conditions, without difficulty, on the first attempt and after the installation of 2 per cent novocaine. The patient's blood pressure at that time was 142 mm. Hg systolic and 74 mm. diastolic. The abdomen was soft. On the day following biopsy the patient's pulse was slightly irregular and the rate was 100 per minute. There was also slight impairment to percussion, with some diminution of breath sounds in the right chest base area. The abdomen showed slight diffuse tenderness and distention. The patient had two attacks of vomiting. On October 30, two days following the biopsy procedure, the patient showed moderate abdominal distention, marked diffuse tenderness and loss of peristalsis. A clinical diagnosis of peritonitis was made and the patient placed on antibiotic and supportive therapy. The white cell count rose to 39,500, with 81 per cent segmented and 8 per cent

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From the Laboratories of The Mount Sinai Hospital of Philadelphia.

nonsegmented polymorphonuclear cells. Despite therapy, the patient became rapidly worse. She showed evidences of marked toxemia, her temperature rose terminally to 104° (rectally), and she died on November 1, four days after liver biopsy.

The autopsy showed a marked extensive peritonitis, with 2,000 c.c. of bile-stained fluid in the peritoneal cavity. This fluid gave a strongly positive reaction to tests for bilirubin; in its sediment were numerous cholesterol crystals. Culture of the fluid showed *Escherichia coli* and *B. subtilis*. The entire liver surface was covered with a thick, yellow, shaggy exudate. The liver biopsy sites in the skin and dia-

FIG. 1. Showing track and area of necrosis produced by liver needle biopsy (×35).

phragm were scarcely detectable. In the right lobe of the liver there was a round, darkly colored opening, 2 to 3 mm. in diameter, from which bile could be expressed on pressure. This was evidently the site of the biopsy puncture. The puncture track extended 1.0 cm. into the liver parenchyma. A microscopic section of this necrotizing track is shown in figure 1. In its course the track traversed a prominent bile duct lying near the surface of the liver. We believe that leakage originated from this duct, with resultant peritonitis. The common bile duct was markedly dilated and thickened. It contained a large, oval-shaped mass of pultaceous, soft material, at the

ampulla of Vater, which occluded the duct in "ball valve" fashion. Also present was a tiny cholecystoduodenal fistula with a lumen only 2.0 mm. in diameter.

Comment

This report demonstrates that the complication of bile peritonitis following liver needle biopsy is more than a theoretic possibility. It may be conjectured that the leakage of bile in this instance was favored by the considerable intraductal biliary pressure which followed upon the occlusion of the common bile duct by the large stonelike mass of pultaceous material found at the ampulla of Vater. This greatly elevated biliary back pressure was probably responsible for maintaining patent the track of the liver biopsy, after the cholangiectatic duct had been accidentally traversed. This established, in effect, an intrahepatic biliary sinus.

Summary

A case of death from bile peritonitis following upon liver needle biopsy is reported. This appears to be the first of its kind in the recorded literature. The procedure is hazardous in obstructive jaundice because of the likelihood of increased intrahepatic biliary pressure within telangiectatic biliary ducts.

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TERMINAL HYPERTHERMIA FOLLOWING INTRATHECAL STREPTOKINASE ADMINISTRATION IN A CASE OF TUBERCULOUS MENINGITIS *

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Clinicians who have treated tuberculous meningitis readily welcome any suggestion which may improve results of treatment in this grave condition. Since Cathie [1] reported beneficial results in tuberculous meningitis from intrathecal streptokinase (a component of streptococcal fibrinolysin), several British reports [2, 3] have confirmed his opinions. In many institutions in England it has become routine to use this therapy, and the major effect has been a reduc-

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tion in the number of cases which develop elevated intracranial pressure and internal hydrocephalus. It has been assumed that the use of this fibrinolytic enzyme should be prophylactic, in addition to its causing the liquefaction of any fibrinous exudate. It is customary to give it intrathecally with streptomycin at the commencement of treatment. Twenty-four injections are given on alternate days. The British investigators report only minimal toxic effects, consisting primarily of mild temperature elevations and increased cellular response. In this country it has been tried in a few cases after block has occurred, with "some reactions . . . its usefulness and safety for this purpose remain to be determined." [4]

With the hope that we could offer some chance of recovery in treatment of a case of tuberculous meningitis, intensive therapy using the newer chemotherapeutic adjuncts was given.

Case Report

A 42 year old male was admitted to the hospital on April 21, 1951, after spending the night in jail because of suspected acute alcoholism. He was obviously confused and disoriented as to time, place and person. He was unable to coöperate with the examination and was having rather frightening hallucinations. The general appearance was one of acute illness and toxicity. Examination revealed a rectal temperature of 103° F.; pulse rate, 100; respirations, 26; blood pressure, 120/80 mm. Hg. Fine crepitant râles were heard over the right upper lung field anteriorly. There was evidence of a healed, indurated area over the left scrotal region, but there was no evidence of acute vesiculitis or epididymitis. Moderate nuchal rigidity was present. Reflexes were equally hyperactive bilaterally. As far as could be determined in this excited individual, the remainder of the examination was within normal limits.

Laboratory Data: On admission the leukocyte count was 10,200, with normal differential. Hemoglobin was 14.1 gm. per cent. Urinalysis was normal. The spinal fluid pressure was 180 mm. water with normal dynamics; it revealed the following chemical values: glucose, 20 mg. per cent; protein, 110 mg. per cent; chlorides, 468 mg. per cent. The fluid was positive for globulin and the cell count was 74 per cu. mm., of which 52 were polymorphonuclears and 22 were lymphocytes. The CO_2 combining power of the blood was 25.9 mEq./L. Blood urea nitrogen was 14 mg. per cent, and blood serology was negative. Blood serum studies for the common encephalitides were negative. Bacteriologic examination of the spinal fluid, including culture for acid-fast organisms, was negative. (Autopsy of a guinea pig inoculated with spinal fluid on April 21 revealed characteristic findings of tuberculosis.)

Roentgenogram of the chest on admission revealed a patchy infiltration in the right apical region, with elevation of the right interlobar septum.

Past History: The patient was found to have had active pulmonary tuberculosis in 1945 while in the Army. He was discharged from an Army hospital after six months of bed-rest, and remained well until January, 1949, when he had an acute upper respiratory infection. He was hospitalized when his sputum was reported positive for acid-fast organisms. He was started on streptomycin, 0.5 gm. daily, and when he was found to have a draining left epididymal mass the dosage was increased to 1.0 gm. daily. Beginning in August, 1950, he was given para-aminosalicylic acid, 9.0 gm. daily. The combined streptomycin-para-aminosalicylic acid therapy was continued until March, 1951, when it was felt that the tuberculous infection, both pulmonary and genitourinary, was inactive. The patient was allowed weekend passes,

and was being considered for discharge from a nearby sanatorium when he was brought to the hospital.

Hospital Course: Considering the history of the case and findings on admission, the following chemotherapy was begun: 1.0 gm. streptomycin intramuscularly and 0.05 gm. intrathecally daily, plus para-aminosalicylic acid, 12.0 gm. daily orally. Other therapy was supportive, consisting of high liquid caloric diet with vitamin supplements. After two weeks of daily intrathecal injections of streptomycin, the dose of 0.05 gm. was given every other day. However, there was little to indicate any response to the treatment, and the patient remained semicomatose, not responding to questions or painful stimuli. He continued to exhibit Cheyne-Stokes respiration, and the nuchal rigidity increased. A graphic recording of the spinal fluid changes and other aspects of the case is shown in figure 1. Spinal fluid pressure remained moderately elevated and there was never evidence of block. A coagulum formed from the fluid for the first time on May 1; the fluid remained clear.

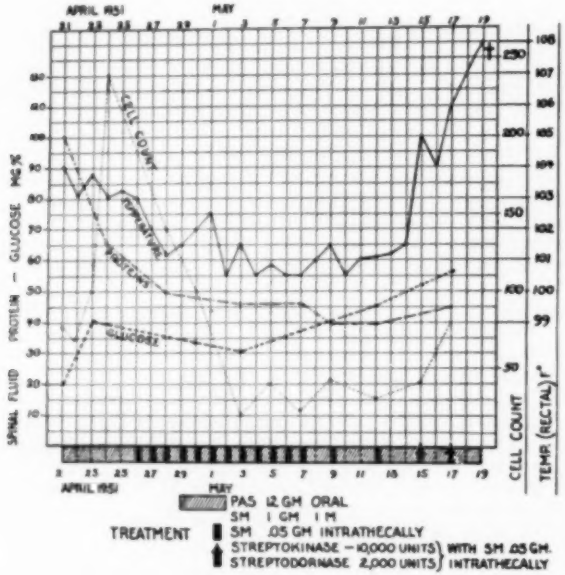

FIG. 1.

On May 15 intrathecal streptokinase (10,000 units) and streptodornase (2,000 units) were given, in addition to streptomycin, 0.05 gm., according to the protocol furnished by the manufacturers of the drugs (Lederle). About six hours after the initial administration of the enzymes the rectal temperature rose to 106° F., but fell to 104° F. by the time of the second injection, on May 17. Again there was marked rise of the temperature to 108° F., despite the usual endeavors to control the pyrexia. The patient died on May 19. Spinal fluid chloride was little changed during the hospital course, the final recording being 500 mg. per cent on May 17; the examinations of the fluid revealed a positive Pandy test on each occasion. Repeated blood

chemical values were within normal limits, including those for non-protein-nitrogen, serum potassium, serum sodium, serum calcium and carbon dioxide combining power. The leukocyte count rose steadily to a level of 17,500, with 93 per cent polymorphonuclears on May 18.

Autopsy Findings: The pathologist reported the findings consistent with general miliary tuberculosis. Tubercles were found in the leptomeninges, lungs, lymph nodes, testicles and seminal vesicles. There were no tubercles in the cerebral substance. There was minimal accumulation of exudate over the surface of the brain, and the brain substance was edematous, with moderate flattening of the convolutions and obliteration of the sulci. There was no obstruction between the ventricular and the subarachnoid systems, and no evidence of hydrocephalus. The microscopic examinations confirmed the diagnosis of widespread tuberculous involvement.

Comment

It is obvious to all that the treatment of tuberculous meningitis in adults is far from satisfactory, but as yet we can offer no single treatment. The feasibility of treating the condition without intrathecal streptomycin has been under study at Fitzsimons Army Hospital.[5] There is very little secretion of streptomycin into the spinal fluid when the meninges are normal. When the meninges become inflamed, however, there is a rise of the streptomycin level in the spinal fluid in patients who are receiving streptomycin intramuscularly. If this fact could be definitely established there would be the freedom from the irritating effects of intrathecal streptomycin. Certainly the use of streptokinase would not be indicated except for the reasons advocated by the British clinicians.

Although our patient had received considerable chemotherapy for months prior to his terminal hospitalization, in the form of many injections of streptomycin and oral para-aminosalicylic acid, he developed a fulminating case of tuberculous meningitis. Considering the rapid onset of the meningitis, intensive therapy, including the use of intrathecal streptokinase, seemed in order. We feel that the fibrinolytic enzyme combination must have been the cause for the terminal hyperthermia. We might add that in subsequent cases of tuberculous meningitis we have not considered it advisable to use this adjunct, despite the claims of the clinicians abroad. Perhaps other reports will bear out our views.

Summary

A case of tuberculous meningitis treated with intensive therapy, including intrathecal streptokinase-streptodornase, has been presented. It is felt that the use of the fibrinolytic enzyme combination was the direct cause of the terminal hyperthermia.

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RELIEF OF PAIN IN ACUTE MYOCARDIAL INFARCTION BY PROCAINE BLOCK OF THE SYMPATHETIC NERVE SUPPLY *

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MANDL in 1925 was the first to use procaine block for the relief of cardiac pain. Swetlow [2] in 1926 introduced the use of alcohol for longer lasting relief by a chemical block. In America this procedure was perfected and popularized by White.[3] Alcohol blocks, sympathectomy and rhizotomy are accepted procedures in general use today for the relief of angina pectoris. We have been unable, however, to find in the literature any reference to the use of sympathetic block for the relief of the pain in acute myocardial infarction. The dramatic relief of pain in a patient with acute coronary occlusion with posterior wall myocardial infarction prompted the report of the following case:

CASE REPORT

A 55 year old male physician first experienced cardiac symptoms in February, 1947, when he became aware of premature contractions. He was otherwise asymptomatic until June 7, 1947, when he suffered an attack of substernal pain while walking on the street. The pain radiated to both shoulders but not down the arms, and lasted about three minutes after he stopped walking. Two days later, while on an airplane trip, he suffered a recurrence of substernal pain which radiated down the left arm and was accompanied by mild dyspnea. The distress cleared after about one hour. He spent the subsequent week at a meeting and took walks up to two miles. Several attacks of substernal pain during the week were relieved by nitroglycerin. He returned to his home on June 19 and consulted his physician, who obtained an electrocardiogram which revealed deeply inverted T waves in the chest lead characteristic of anterior wall ischemia (figure 1). He was treated by bed-rest at home for three weeks; following this, his activity was gradually increased and on September 1 he resumed his usual professional activities. During the next nine months he was conscious of occasional premature contractions. For the two and one-half years after his first attack he had no angina of effort but experienced substernal distress on excitement; because of this, he refrained from attending athletic contests and, later, from listening to broadcasts of them over the radio.

On November 30, 1949, he experienced substernal pain while walking a distance of two city blocks against a cold stiff wind. The pain disappeared spontaneously when he stopped walking and entered a corner store. During the next 10 days he had paroxysmal pain, noted chiefly in the left shoulder and left arm and relieved by nitroglycerin and rest. From December 5 to 8 he attended a surgical convention and was conscious of anginal distress several times a day during this period, despite the fact that he restricted his activity considerably. He returned home on December 9 and at 6:00 p.m., while sitting down, was seized with an agonizing substernal distress. The subsequent events are best described in his own words.

"A particularly severe attack of anginal pain started at 6:00 p.m. The pattern was somewhat atypical, inasmuch as the most severe agonizing pain occurred in the

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From the Departments of Internal Medicine and Surgery of the University of Louisville School of Medicine.

left arm deep beneath the biceps muscle and in the left subpectoral region. The substernal pain was relatively mild. Nitroglycerin (sublingual), 1/200 gr. at 15 minute intervals, failed to give relief. After about 45 minutes of gradual mounting distress, a physician was called. On arrival at 7:30 p.m. he administered 1/6 gr. of morphine subcutaneously and arranged for my admission to the hospital. The morphine gave no relief.

"On admission to the hospital at 8:25 p.m. a second subcutaneous injection of morphine sulfate, gr. 1/6, was given. This was no more effective than the first. Oxygen gave no relief. I then received pantopon, gr. 1/3, intravenously at 9:20 p.m. I still had no relief; in fact, the pain was mounting in fury. At this time the pain was radiating into both arms, although it was dominant on the left side. The radiation of pain was characteristically along the arterial blood supplies, subclavian, axillary, brachial, radial and ulnar arteries. The pain did not follow the somatic nerve supply (i.e., the ulnar distribution).

"After approximately two and a half hours of this intractable distress, I could feel myself slipping over the borderline into a state of shock."

At this point a procaine injection in the region of the stellate ganglion was performed through a supraclavicular approach using 1 per cent procaine. The results as expressed in the patient's own words were:

"Not more than 2 or 3 c.c. of procaine had entered the vicinity of the stellate ganglion before I experienced a pleasant warm sensation down the left arm. Within a few seconds, the pain in the arm had completely subsided. Next, the subpectoral pain disappeared and last, the substernal pain. Within less than three minutes I was completely comfortable."

Physical Examination: Physical examination at 7:30 p.m. on December 9, 1949, revealed the following pertinent findings: In spite of his severe pain, the patient was not orthopneic or dyspneic. The skin was warm and dry. There was no cyanosis. The blood pressure was 160/86 mm. of Hg; temperature, 98.2°; respirations, 16; pulse 73. Funduscopic examination revealed some narrowing of the retinal arterioles and exaggeration of the light reflex, but no AV compression or other abnormalities. The venous pressure, as estimated by inspection of the external jugular veins, was within normal limits. The thyroid gland was normal to palpation. The lung fields were clear to percussion and auscultation. The cardiac apex impulse was not palpable. There was no enlargement to percussion. The rhythm was regular, rate 73. There were no murmurs or pericardial friction rub. A_2 was moderately accentuated. The liver and spleen were not palpably enlarged. There was no edema of the lower extremities. The dorsalis pedis and posterior tibial pulsations were normal. The brachial and radial arteries were moderately thickened and tortuous. The reflexes were physiologic.

Laboratory Studies: Laboratory studies on admission were as follows: Leukocytes numbered 9,050, with a differential count of 68 per cent polymorphonuclear leukocytes, 3 per cent monocytes and 29 per cent lymphocytes. Erythrocytes numbered 4,310,000; hemoglobin, 13 gm. Urinalysis: specific gravity, 1.017; albumin, negative; sugar, negative. Microscopic: a very occasional white blood cell, otherwise no abnormalities. Prothrombin time, 105 per cent of normal. Coagulation time, 2 minutes and 35 seconds. Serum cholesterol, 160 mg. per cent. Sedimentation rate, 24 mm. in one hour. An electrocardiogram revealed ST segment elevation in Leads II and III, and ST depression in Leads CF_2 and CF_4. On December 10 an electrocardiogram (figure 1) revealed additional changes diagnostic of infarction of the posterior wall of the left ventricle, consisting of a deep (3 mm.) Q_2 and 4 mm. Q_3, with deep inversion of T_2 and T_3.

Subsequent Course: Within three hours of the procaine block, the pain recurred and was again relieved by a stellate block. This procedure was repeated 12 times

within 36 hours, at which time all pain ceased. The duration of the effectiveness of the blocks varied between two and a half and four hours. On several occasions after the injection of 1 c.c. of procaine, a Horner's syndrome developed and was accompanied by an immediate disappearance of the pain.

Anticoagulant therapy was commenced at the time of admission. Dicumarol, 300 mg., was given orally. This was followed by 200 mg. of Dicumarol on December

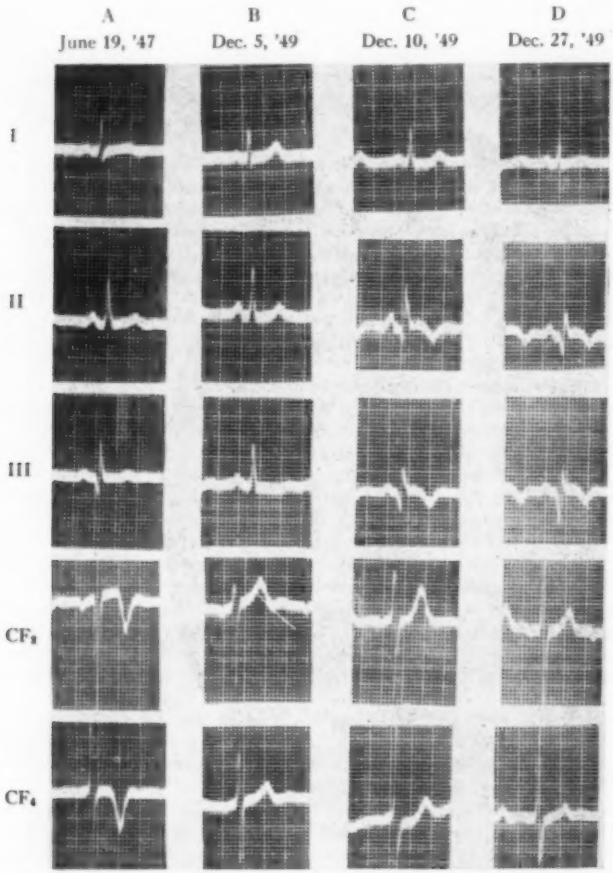

FIG. 1. *A*. Electrocardiogram during first episode, revealing evidence of anterior wall ischemia.

B. Electrocardiogram four days before onset of present episode, revealing complete normalization of previous changes.

C. Electrocardiogram 24 hours after onset of present episode, revealing typical early changes of acute posterior wall infarction.

D. Electrocardiogram approximately three weeks after onset, revealing progressive changes of posterior wall infarction.

10 and 100 mg. on December 11. On December 12 the prothrombin time reached 15 per cent of normal, and subsequently remained between 20 per cent of normal and 28 per cent of normal on a dose which averaged 25 mg. per day.

Following the subsidence of pain on December 11, the patient's course was essentially uneventful until December 15, when he developed dull precordial aching, mild orthopnea and a loud pericardial friction rub which was audible over the entire anterior chest wall and which persisted for three days. Inspiratory basal râles also appeared at this time. On December 19 the patient developed auricular fibrillation, increasing dyspnea, basal râles and moderate hepatic enlargement. Pallor became noticeable and the patient passed a tarry stool. The red blood cell count on this date was 2,900,000; hemoglobin, 8.5 gm. The prothrombin time was 20 per cent of normal. Dicumarol was omitted and synthetic vitamin K, 70 mg., was given with no change in the prothrombin time. It was felt that the anemia was an important factor in the deterioration of the patient's condition, and a 250 c.c. whole blood transfusion was decided upon. When the patient had received 100 c.c. of blood, he suddenly developed a chill and severe dyspnea, necessitating the discontinuance of the transfusion. Digoxin was administered, in doses of .5 mg. to .25 mg. daily, between December 19 and December 22. The rhythm reverted to normal on December 21. The patient remained dyspneic, however, despite continuous oxygen therapy and diuretics, and the anemia persisted. On January 1, 1950, the red blood cell count was 2,050,000; hemoglobin, 9.5 gm. Another attempt to correct the anemia by transfusion of whole blood resulted in an episode of acute left ventricular failure just as a transfusion of 250 c.c. was being terminated. The dyspnea responded to intravenous aminophylline. Three hours later, auricular fibrillation developed and was accompanied by an increase in dyspnea and pulmonary râles. He was placed on quinidine sulfate, 3 gr. every four hours, and the auricular fibrillation reverted to normal sinus rhythm on January 6. Thereafter, his course was one of gradual improvement, and on January 20 he was allowed to return home. He tolerated well a gradual increase in physical activity, and returned to practice (limited to consultations one hour daily) on June 1. He is, to the present time, asymptomatic and requires no medication.

Discussion

It is generally understood that the chief aim of any neurosurgical procedure for the treatment of cardiac pain is the interruption of the sensory supply to the heart. The question of whether vasoconstrictor impulses can be blocked or whether there is improved circulation to the heart muscle following a block has not yet been decided. In fact, there is still disagreement as to the pathways of both the sensory and the vasomotor fibers.

It is now accepted that the majority, at least, of the afferent pain-conducted fibers pass through the inferior cervical and the upper two or three thoracic ganglia.[4] Lindgren,[5] who studied a large series of cases of angina pectoris following sympathectomy, states that, after a bilateral operation removing these ganglia, 100 per cent of the patients were relieved of their arm pain but some chest discomfort persisted in 20 per cent of the cases. In these cases he assumed that sensory fibers pass elsewhere than through the stellate and thoracic cardiac nerves, or that new afferent fibers which have not previously carried cardiac pain take over the function. In the treatment of angina pectoris, it has been found that if the pain is predominantly on the left side a unilateral procedure will suffice in the majority of the cases. In a few, the pain will then become more prominent on the right side, and a bilateral procedure will become necessary.

For the treatment of the pain in acute coronary occlusion, therefore, it is possible that a bilateral stellate block would be necessary for the total relief of pain. In the present case, although there was some pain bilaterally, the predominant and most severe pain was in the left chest and arm. The left stellate block, however, promptly relieved all of the pain.

Since there is disagreement as to whether the thoracolumbar sympathetic carries vasoconstrictor, vasodilator or perhaps both vasoconstrictor and vasodilator fibers, no definite conclusions can be reached as to the effects of temporary sympathetic denervation on the course of the pathologic process in the heart. Most of the teaching has been that the sympathetic carries vasodilator fibers and the vagus or parasympathetic carries vasoconstrictor.[6] This theory is not accepted by some workers. Even if the thoracolumbar sympathetic carries chiefly vasoconstrictor fibers, as stated by Katz and Jochim [7] and by Leriche and Fontaine,[8] it is doubtful that there would be significant improvement in the circulation in one whose coronary artery had become occluded, unless it would be from relief of reflex vasospasm in unoccluded portions of the coronary tree. Lindgren [5] states specifically that there is no evidence of any damage to the cardiac circulation through cervicothoracic ganglionectomy in their group of cases operated upon for angina pectoris.

The anterior or supraclavicular approach for the stellate ganglion injection is especially suited for a patient with acute myocardial infarction, since the patient does not have to be turned on his side. It is easily performed, with virtually no pain to the patient. One of the authors has performed hundreds of stellate blocks for other conditions without encountering a complication.

While the factor of pain is variable in individuals who sustain an acute myocardial infarction, and while in many instances opiates afford satisfactory relief of the pain, there remains a group (of which this patient is an example) where standard methods of treatment, including opiates and oxygen therapy, fail to alter significantly the intensity of the pain. In such cases the persistence of intensive pain, with the associated stress, anxiety and sense of impending dissolution, may well be the deciding factor in survival during the early hours after infarction. In this patient, the total relief of pain immediately following stellate block, together with the confidence that recurrences of the pain could be immediately and completely relieved, was accompanied by a disappearance of the strong emotional factors previously present.

The striking benefits accrued as a result of this simple procedure in this patient warrant consideration of the use of stellate block wherever pain due to acute myocardial infarction fails to respond to standard methods of treatment.

Summary

1. We have reported the immediate relief of pain in the initial stage of acute coronary occlusion with posterior wall infarction by means of procaine blocks of the left stellate ganglion.

2. Certain of the physiologic and clinical aspects of the procedure are discussed.

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FOOD ALLERGY WITH SPECIAL REFERENCE TO CORN AND REFINED CORN DERIVATIVES *

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At a hearing on "Bread Standards," held during the summer of 1949 before the Federal Security Administrator, consideration was given to the possible allergenic ingredients of bread, including corn and the refined corn derivatives. The testimony revealed a sharp difference of opinion regarding the incidence of sensitiveness to corn among the allergic population. The divergence was so marked as to justify an inquiry into the present status of allergy to corn and to present additional and pertinent experimental evidence.

Dr. Theron G. Randolph testified that corn was second only to wheat as a specific cause of chronic food allergy. He stated, moreover, that one out of every five of his new patients (or 20 per cent) was found to be corn-sensitive. Confirmation of this high incidence came from the reports of Zeller and Rowe. Zeller had encountered 30 to 40 corn-sensitive patients during the past year, whereas Rowe had found 20 to 35 per cent of 1,200 patients allergic to corn.

Randolph and Yeager,[1] in a later publication, not only reëmphasize the high incidence of corn sensitivity but also include some of the refined corn derivatives as causes of corn allergy. In treatment, they recommend the avoidance of corn starch, corn sugar and corn syrup. They even urge a careful investigation of the current widespread use of corn syrup in infant feeding, implying thereby that corn syrup may become a sensitizing factor in infancy. "Corn is, by all means, the most difficult food in the American diet to avoid," these authors assert. If, therefore, 20 per cent of our allergic population are to be adequately protected, they must be denied an important food and its derivatives which are omnipresent in the American diet. Moreover, the widespread use of corn starch and corn sugar in such unsuspected articles as milk cartons, frozen food containers and excipients presumably adds to the menace.

At the hearing, dissenting opinions regarding the alleged high incidence of sensitiveness to corn were voiced by five allergists. Rawling, in a study of 1,250 case records, discovered only 15 patients (or 1.2 per cent) with corn sensitivity, indicated either by skin or by ingestion tests or both. Sheldon testified that he had given corn starch, corn sugar, corn syrup and corn oil to six patients proved

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clinically sensitive to corn meal by the ingestion test. He was unable to produce allergic symptoms by feeding the corn products. Cazort's findings were identical with those of Sheldon in feeding corn starch, corn oil and corn syrup to two patients very sensitive to corn meal. Halpin had encountered approximately 15 patients clinically sensitive to corn meal from 1946 to 1949. During this period he had seen, on an average, 350 to 400 new patients each year. Feeding tests performed with one corn-sensitive patient by the "blindfold" technic failed to reveal a sensitiveness to corn starch and dextrose. Rawling also reported that the experimental feeding of corn starch, corn syrup and corn oil to a corn-sensitive patient provoked no allergic reaction. In summary, it may be stated that four allergists have been unable to reproduce symptoms by the experimental feeding of corn derivatives to a total of 10 patients sensitive to corn meal.

The findings from a questionnaire which had been submitted by Dr. Mary H. Loveless to experienced allergists of the country also assume significance. Nineteen physicians reported that they had tested within a recent five year period approximately 35,826 patients for sensitiveness to corn meal and that, among this number, 56 cases had been found clinically sensitive to corn, the percentage being 0.12. Furthermore, the experience of Walzer, as indicated in his reply to the questionnaire, is noteworthy. He writes: "Corn meal reactions are frequent, and may be strongly positive. . . . Reactions to corn by passive transfer are as common as by direct testing. . . . Corn starch reactions are extremely uncommon, even when strong corn meal reactions are obtained. We can recall only one corn starch reaction obtained by passive transfer, despite the high number of corn meal reactions obtained with this technic."

Our experience also shows that the incidence of cases with significant symptoms of sensitivity to corn or to corn derivatives has been very much lower than that recorded by Randolph, Zeller and Rowe. In an analysis of 2,431 patients under my observation and tested for corn, 301 (or about 12 per cent) gave positive cutaneous reactions. Of 306 patients who associated some of their symptoms with sensitiveness to foods, nine (or about 3 per cent) attributed their distress to the ingestion of corn.

A recent noteworthy contribution to the study of foods in respiratory allergy has been made by Leibowitz, Chester and Markow.[2] These authors performed 3,920 skin tests by the intracutaneous method with 56 individual food extracts on 70 patients. The skin tests, irrespective of their results, were followed by intentional feeding tests with all the foods employed. Each food was eliminated from the diet of the patient for one week prior to the ingestion test. Thirty-three of the 44 patients who showed a positive skin test with corn were subjected to the feeding test, with two positive reactions. In the case of the 26 patients who reacted negatively to the skin test, 15 feeding tests with corn all proved negative. Thus, two patients in a total of 48 (or 4.1 per cent) gave evidence of clinical sensitiveness to corn by the ingestion test. Only one patient, however, in a total of 54 (or 1.8 per cent) reacted positively to the ingestion test with corn meal. In this latter group, there were 37 positive and 33 negative skin reactors. The authors conclude that food plays a minor rôle in the causation of respiratory allergy. The discrepancy in the incidence of corn allergy as shown by the foregoing reports was, indeed, as distressing as it was challenging.

The purpose of the present study is to supplement the one I have previously

made and to determine the incidence of sensitiveness to corn derivatives among those found to be sensitive to corn meal by the application of the Randolph technic.

The limitations of clinical history and of skin tests for the diagnosis of food sensitiveness have been fully recognized. Agreement is universal that the ingestion test offers more accurate and specific means of diagnosis of food allergy. The test food is ingested on a fasting stomach after a period of four days of abstinence from that food. The symptoms provoked by such ingestion are determined by the affected "shock organs"—the respiratory tract, the gastrointestinal tract or the skin. It follows, therefore, that sensitiveness to corn allergens in the corn derivatives—dextrose, corn starch, corn syrup and corn oil —can only be determined by the ingestion test in an individual who has been proved sensitive to corn meal.

In my preliminary experiment,[3] 50 consecutive cases were subjected to the ingestion test with corn meal following a prescribed preparatory period. Only two of my patients (or 4 per cent) reacted positively. Despite the small series, the findings are significantly low. The supplementary phase of the study, that of sensitiveness to corn derivatives, was made possible by the unusual coöperative effort of one of my patients.

Case History

The subject who coöperated in the present investigation was a 37 year old woman with a history of allergy on the paternal side. Her chief complaint was asthma of 11 years' duration. The symptoms were perennial and were aggravated from July to October. Provocative causes were "taking cold," excitement, emotional stress and fatigue. Exposure to drafts, air-cooled environment, electric fans and dust "choked her up." She was sensitive to aspirin and to the iodides: the former produced "indigestion," the latter pain in the jaws, as if she had mumps. The eating of corn and lima beans was immediately followed by choking sensations. The symptoms were prompt in appearance, and she adds: "The first spoonful of corn will choke me up." In fact, the steam arising from boiling corn would excite an asthmatic paroxysm, whereas steam from other foods had no deleterious reaction. Eating corn starch custards would produce symptoms which were "not real bad." She had not used corn oil or syrup. She was fond of corn and lima beans but had excluded these foods from her diet because of their ill effects.

During the initial visits of our patient to the clinic, cutaneous tests for protein sensitivity were performed as a matter of routine. Of all inhalant allergens, the pollen of the English plantain reacted positively. The food extracts, including corn, gave negative reactions. With the renewal of our interest in her clinical sensitiveness to corn and possibly to derivatives of corn, a revised list of potential allergens was used on August 9, 1949, for the determination of skin sensitiveness. The list was comprised of the following: corn meal (Indian Head), corn meal (Mammy Lou), corn oil, corn starch (Argo), allergen extract of corn meal, cottonseed oil, rye flour and whole wheat. The eight test substances were applied to scratches on the skin of each thigh. The site of the corn starch presented an areola which gave rise to a slight itching sensation. All the other tests were negative. Again on April 28, 1950, two extracts of corn meal and zein, in powdered form, gave negative skin reactions in a duplicate series. On May 12, 1950, zein was reapplied to scratch marks on the skin, with negative result. The patient was kept under observation for an hour after the test. It is significant that no constitutional reaction ensued in a subject as sensitive as she was subsequently determined to be, by the absorption of the chief protein isolated from corn meal.

Feeding Tests. Results

In the series of feeding experiments in which the patient participated, she was never advised of the nature of the food given to her. Herein is an important modification of the Randolph technic. It was deemed essential to minimize all psychic factors,

On July 12, 1949, the first ingestion test was performed. The patient was instructed to abstain from the consumption of corn, corn products and corn derivatives during the four days preceding the test. A list of permissible foods was furnished, as well as a blank sheet for recording the articles of foods ingested during the preparatory period. On the morning of the test the patient, having been previously admonished not to take any food, drink or medicine, was offered four ounces of warm corn meal mush. After swallowing one teaspoonful of the corn meal she experienced an itching of the lips and immediately developed severe asthma. The administration of 0.4 c.c. of adrenalin and of 7.5 gr. of caffeine sodium benzoate brought gradual and complete relief.

Table 1 lists nine experimental feeding tests, performed with corn meal mush, corn starch pudding, corn oil, corn syrup, arrowroot pudding and peanut oil. Each feeding test with a corn derivative was repeated at a subsequent time. The test

Table I

Feeding Tests; Identity of Food Unknown to Patient

Date of Feedings	Ingestant	No. of Feedings	Reaction
1949			
July 12	Corn meal mush	1	Asthmatic attack
July 26	Corn starch pudding	1	Asthmatic attack
July 29	Arrowroot pudding	1	Negative
Aug. 5	Corn starch pudding	1	Asthmatic attack
Aug. 10	Peanut oil	1	Negative
Aug. 12	Corn oil	1	Negative
Aug. 26	Corn oil	1	Negative
Sept. 2	Corn syrup	2	Negative
Nov. 22	Corn syrup	2	Negative

feeding with each article was performed on a fasting stomach after a four-day period of abstinence from the derivatives of corn. The identity of the test food was not disclosed to the patient.

The ingestion of corn starch on July 26 and August 5 was followed by asthmatic attacks in 18 and 15 minutes, respectively. The administration of adrenalin was necessary to bring relief. The ingestion of 20 c.c. of peanut oil, of four ounces of arrowroot pudding, of 30 c.c. of corn oil and of 60 c.c. of corn syrup at two different trials was not followed by allergic disturbances.

Table 2 includes six feeding experiments with puddings, the identity of which remained unknown to me until after the completion of the series. Four ounces of pudding were consumed at each serving. Two feedings of arrowroot pudding and one of potato starch pudding gave rise to no symptoms. Two feedings of tapioca pudding and one of corn starch provoked asthmatic seizures which required the injection of adrenalin for relief. This second series of experiments not only confirmed the patient's sensitiveness to corn starch but also disclosed a sensitiveness to tapioca. Interestingly enough, when advised of this unexpected finding the patient commented that she had not eaten tapioca to her knowledge for at least 20 years.

In the period from July 22, 1949, to February 21, 1950, the following 15 feeding

tests were performed with our patient: one with corn meal mush, three with corn starch pudding, three with arrowroot pudding, two with tapioca, one with peanut oil, one with potato starch, two with corn oil and two with corn syrup. The corn meal mush, the corn starch and the tapioca were regarded as allergenic offenders because, upon ingestion, each gave rise to asthmatic symptoms. Ingestion of corn oil and corn syrup, arrowroot pudding, peanut oil and potato starch did not produce allergic manifestations. The ingestion tests were all performed on a fasting stomach after a preparatory period of abstinence from corn and corn derivatives.

The above tests emphasize the limitations of cutaneous testing for food sensitiveness and indicate that cutaneous sensitiveness and mucosal sensitiveness are distinct entities.[4] This difference was illustrated when some powdered corn starch was applied on the inside of the lower lip of our subject. Within a very few minutes she began to "choke up." Thirteen minutes later, the starch was removed and the mouth rinsed. There was a gradual subsidence of her discomfort. One week later, a large granule of starch was placed on the inside of the right cheek. Slight coughing ensued. Fifteen minutes later, the coughing was accentuated, and breathing became labored. After 65 minutes, the starch was a paste, the mucosa was normal in appearance and the dyspnea had increased, necessitating the use of adrenalin. The

TABLE II

Feeding Tests; Identity of Food Unknown to Dispenser and Patient

Date of Feedings	Symbol	Ingestant	Reaction
1950			
Jan. 25	E 1	Tapioca	Asthmatic attack
Feb. 3	F 1	Arrowroot pudding	Negative
Feb. 7	C 1	Potato starch	Negative
Feb. 10	F 1	Arrowroot pudding	Negative
Feb. 13	A 1	Corn starch	Asthmatic attack
Feb. 21	E 1	Tapioca	Asthmatic attack

patient reported that later on in the afternoon she experienced a feeling of soreness on that portion of tongue and cheek which had been in contact with the starch granule. She also noted in that area four "small blisters" which disappeared by morning.

The determination of a reagin for corn in the blood serum of our subject was next undertaken. Seven individuals were each sensitized with her blood serum and with 0.05 c.c. of serum from a cottonseed-sensitive patient as a control. The sensitized sites of four recipients were each tested by intracutaneous inoculation with a corn extract. The results were negative.

The other three recipients were subjected to a feeding test. Six ounces, eight ounces and 10 ounces of corn meal mush respectively, were consumed by each person on a fasting stomach. The skin sites, sensitized with the serum from our corn-sensitive patient, remained unchanged. Thus, by feeding test and direct testing of sensitized sites, there was disclosed no evidence of a specific reagin for corn meal. The recipients were instructed to abstain from eating corn and corn derivatives for a period of four days prior to sensitization and for three days following inoculation with the test sera.

The allergen in the corn meal, whatever its nature may be, exerted no harmful influence upon the gastric mucosa. It caused no nausea, vomiting or diarrhea. The allergen was readily transported by the blood stream to the reactive or sensitized cells of the respiratory tract, with resulting upheaval.

Discussion

Consideration must now be given to the alleged potential allergenic properties of corn derivatives—dextrose, corn starch, corn syrup and corn oil. Randolph's views [5] are summarized in his testimony as follows: "The treatment of food allergy consists in the complete avoidance of the specific foods diagnostically incriminated; in the majority of instances when dealing with the high degrees of sensitivity this means the avoidance of the particular food in its native form, as found in the native form cooked and in addition fractions of the food such as the starch and sugar derived from that food. In some instances it is also necessary to avoid the oil of the food in question in order to relieve specific allergic symptoms. . . . In the first 100 cases, corn sensitivity was diagnosed by feeding canned corn or corn meal gruel. In the second group of 100 cases, corn meal gruel plus corn sugar was used as the test food. The results of these two series indicate that the addition of corn sugar increased the incidence and severity of allergic symptoms occurring during the course of experimental food tests for detection of corn sensitivity."

It is evident from current practice that the allergenicity of corn sugar or glucose has been totally disregarded. The intravenous administration of 1 to 3 L. of a 10 per cent solution of glucose to dehydrated asthmatic patients has frequently proved to be a life-saving measure.[6] It has been our routine practice to have patients drink a solution of dextrose in warm water after an injection of adrenalin for the control of an acute paroxysm. No untoward reaction has been encountered to warrant a change in clinical procedure. In fact, the drinking of a solution of approximately 34 gm. of glucose in water, and even the intravenous administration of a 50 per cent glucose solution with aminophylline, helped alleviate rather than exaggerate severe asthmatic paroxysms in our patient. Tuft's [7] conclusion, that the intravenous use of hypertonic glucose seems to be a valuable adjunct in the treatment of acute severe asthmatic paroxysms, has found universal acceptance. This is significant because of the belief that the problem of corn sensitivity is not limited to certain geographic regions. Therefore, many of the 20 per cent of allergic patients presumably corn sensitive have inevitably received and will continue to receive some form of intravenous glucose therapy at critical stages of their disease. The report of Randolph, Rollins and Walter [8] on allergic reactions following the intravenous injection of corn sugar commands attention. These authors have selected four of several patients shown to be highly corn-sensitive and have administered intravenously 25 c.c. of 5 per cent dextrose solution in each case. Severe constitutional reactions ensued which were clinically similar to those following the ingestion of corn sugar and corn meal. Because of the extensive use of dextrose solutions in treatment, the potential dangers above indicated cannot be minimized, and confirmation is most essential. Nevertheless, one important point must not be overlooked. In the course of desensitization with an extract of an offending allergen, every precaution is taken to prevent accidental intravenous injection with the extract.[9] The results may be dire. Therefore, the intravenous testing of human subjects with a suspected allergenic solution should be undertaken with extreme care, if at all.

As previously noted, three feeding tests with our patient revealed her sensitiveness to corn starch pudding with the production of an asthmatic attack. A

similar reaction followed the application of corn starch granules to the buccal mucosa. Two possible sources of the protein responsible for these positive reactions may be offered in explanation. First, some of the residual protein in corn, about 0.3 per cent on a dry basis, calculated as nitrogen, may be left over on separation of the starch from the gluten water. However, much of this protein is denatured because of the high heat employed in the drying of starch. Second, ordinary commercial starches are not entirely bacteria-free. Contamination resulting from exposure of starch to air and water may occur on the way to the final consumer. The protein residues detectable in corn starch may originate in bacterial cells or enzyme fragments which remain in the starch granules.[10] It is noteworthy, indeed, that Walzer reported one case of sensitiveness to corn starch, whereas Rawling, Sheldon, Halpin and Cazort have not encountered such a case in their study of 10 corn meal-sensitive patients.

Moreover, the consumption of corn oil and of corn syrup (see tables 1 and 2) by our highly corn-sensitive patient was followed by no ill effects whatsoever. According to the earlier concepts, the edible oils derived from oil seeds contained the allergen of the parent material. The work of Bernton, Spies and Stevens [11] failed to uphold this tradition. Their work has been confirmed by Mitchell,[12] Figley [13] and Loveless.[14] It is noteworthy that corn oil as exemplified by this experience follows the pattern of being nonallergenic.

Corn syrup is a product of the controlled partial hydrolysis of corn starch. The bulk of the syrup marketed contains about 34 per cent reducing sugar, calculated as dextrose. The protein content is negligible. The amount of nitrogen in corn syrup commonly listed and accepted by the industry is 0.005 per cent. This residual protein in the syrup is probably more thoroughly denatured than that in starch because of the more severe treatment by heat and chemicals in its manufacture.[10] In 1935, Ratner and Gruehl [15] reported an experimental study in which they showed that corn sugar syrup and crystalline sugar, derived from the hydrolysis of corn starch, were not anaphylactogenic for guinea pigs. They accordingly concluded that these products were unimportant in human allergy. Randolph and Yeager dissent. The loss or denaturing of protein sustained in the processing of some food products may render the final product nonallergenic.

Randolph insists upon certain criteria as evidence of a specific allergic reaction to the ingestion of foods. In addition to symptoms referable to the respiratory and gastrointestinal tracts and skin, he lists the sensation of pulling, drawing tightness in the back of the neck, chilling and goose flesh, tachycardia, perspiration and fatigue as positive reactions in food allergy. Opinion on the important question of diagnostic procedure is divided. Those to whom the proposed criteria are not acceptable may test themselves as well as their patients by the "blind-fold technic." The application of the "blind-fold technic" in the diagnosis of food allergy has been fully justified in a study of a case of alleged sensitiveness to cottonseed oil.[16]

It is well to emphasize at this time the criteria, acceptable to Randolph and unacceptable to other investigators, upon which a positive allergic reaction to an ingestion test is based. In the experimental feeding tests conducted with my corn-sensitive patient, an asthmatic attack was the index of a positive reaction. Asthma was the chief complaint of the patient. The respiratory tract constituted the "shock organ." The many minor symptoms, attributed to an allergic

state, are also present in nonallergic conditions and therefore have no decisive diagnostic significance.

Kahn,[17] in a recent discussion of 25 years of experience with food allergy, comments as follows: "Production of symptoms by ingestion of incompatible foods on an empty stomach is of course a requisite from a scientific proof point of view. . . . It is not always possible to secure such confirmation of correctly diagnosed offending foods by dietary resumption on an empty stomach. Patients will not always consent." Another requisite to be added is that deductions be not based on a single observation, positive or negative. This point is well illustrated by Sheldon. He reported that one of his six corn-sensitive patients developed abdominal distress after ingestion of corn starch. When corn starch was mixed with mashed potatoes, concealing its taste, the patient did not have any symptoms. The conclusions to be drawn from our study of a single patient are significant in that they are based upon adequately controlled observations.

A review of the evidence presented herein warrants the following deductions: The provocative ingestion test furnishes a reliable means of diagnosis of food allergy. The suspected food ingested on a fasting stomach must reproduce the allergic symptoms attributed to it. The reliability of the ingestion test is enhanced by excluding or minimizing psychic factors. Sensitiveness to corn meal among the allergic population ranks very low in incidence. Sensitiveness to corn starch is of rare occurrence, presumably among the cases extremely sensitive to corn meal. Sensitiveness to other corn derivatives—corn sugar (dextrose), corn syrup and corn oil—has not been demonstrated by ingestion tests adequately controlled.

The dictum, "The treatment of corn allergy entails the elimination of all sources of corn," is indeed open to question.

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MASSIVE GASTROINTESTINAL HEMORRHAGE IN A CASE OF BOECK'S SARCOID *

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Hemorrhagic manifestations occurring during the course of Boeck's sarcoid are distinctly unusual. In a review of the literature we have been able to find only 10 cases in which hemorrhage has been a prominent sign or has actually been the cause of death. Rubin and Pinner [1] reported a series of 25 autopsies of sarcoidosis from the literature and added a case of their own. Of these 26 cases, two presented purpura as important clinical features. Berblinger is the author of case 9 in Pinner and Rubin's series. His case was that of a 25 year old man who was admitted to the hospital because of iridocyclitis and mediastinal hilar lymphadenopathy. He later developed gingival bleeding and cutaneous ecchymoses. No thrombocytes were seen in the peripheral smear. Right hemiplegia ensued and the patient died. Sarcoid lesions were found in the lungs, spleen, liver, tongue and mediastinal lymph nodes. Death in this case was attributed by the author to "essential thrombocytopenic purpura" with cerebral hemorrhage. It is of interest to note that, although no tubercle bacilli were discovered on section, secondary passage in guinea pigs was positive. The second case in Pinner and Rubin's series was that described by Kraus (case 21). This patient was a 41 year old female with an endocrine disturbance caused by sarcoidosis involving the pituitary stalk and body. The terminal episode was one of epistaxis and serous membrane hemorrhages associated with thrombocytopenia and marked anemia. Sarcoid lesions were found in the lungs, lymph nodes and spleen. Schwartz [2] reported the case of a 16 year old white girl with a subacute purpura of one month's duration. No details were given about platelet counts, but this case is one of 30 cases of thrombocytopenic purpura analyzed with respect to the prognostic value of bone marrow eosinophilia. This patient made an uneventful recovery after splenectomy. The spleen was involved by Boeck's sarcoid, and the author attributes the thrombocytopenic purpura to "overactivity of the diseased spleen." Nordland [3] described a 26

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year old white female with a history of cutaneous ecchymoses and menorrhagia, associated with thrombocytopenia as low as 60,000/cu. mm. The last hospitalizations were for ecchymoses and hematuria occurring during the fifth month of pregnancy. The platelet counts ranged from 25,000 to 250,000/cu. mm. Her hemorrhagic tendency was controlled as soon as the splenic pedicle was ligated. Splenectomy was performed, and the spleen showed sarcoidosis. The patient had an uneventful convalescence, and was delivered of a normal infant at term. Her platelet count six days postoperatively rose to 484,000/cu. mm., and three months later was 464,000/cu. mm. Enzer's [4] case was that of a 32 year old white male who had been under observation for three years because of symptoms suggestive of peptic ulcer. One year later chest roentgenogram revealed bilateral upper lobe fibrosis. Eight months before death the patient developed a pancytopenia in the peripheral blood, while the marrow showed hyperplasia. Purpura appeared and became more severe despite transfusions. Splenectomy was performed, but the patient developed postoperative bleeding and died. Examination of the spleen revealed an enlarged, nodular organ which was filled with sarcoid lesions. Necropsy study showed sarcoidosis of the lungs and lymph nodes. Doan and Wright,[5] in their treatise on the hypersplenic mechanism, listed a single case of Boeck's sarcoid of the spleen as a secondary inflammatory cause of hypersplenism, but no details of the case were included. Ribaudo et al.[6] reported two cases of hemorrhage associated with sarcoidosis. Their first case was an 18 year old Negro female admitted because of epistaxis and a hematoma of the lip. There was evidence of generalized sarcoidosis in the form of preauricular swellings, skin nodules and mediastinal hilar lymphadenopathy. She developed skin purpura, hematuria and hemiplegia. Her platelet count was 570,000/cu. mm. She died on the ninth hospital day. At necropsy, sarcoidosis was found in the mediastinal lymph nodes, lungs, spleen and myocardium. There was extensive hemorrhage in the skin, serous membranes, stomach and small intestine, as well as a large hemorrhage in the basal ganglia extending to the lateral cerebral ventricles. Their second case was a 23 year old white female with a history of recurrent episodes of menorrhagia of five years' duration and ecchymoses of the skin of the extremities for seven years. The only hematologic abnormality was a platelet count of 100,000/cu. mm. After splenectomy, the platelet count rose progressively to 329,000/cu. mm. and the hemorrhagic manifestations disappeared. The spleen showed the presence of sarcoidosis. One month postoperatively the platelet count dropped to 140,000, but the patient had no further purpura or menorrhagia. Ricker and Clark [7] analyzed 300 consecutive cases of sarcoidosis from the files of the Army Institute of Pathology. There were 22 necropsies in their series, and only two cases demonstrated any hemorrhagic tendencies. Their case 5 was a 22 year old Negro who was hospitalized because of epistaxis of two days' duration. There was a past history of frequent nosebleeds. Two days after admission, the patient lapsed into coma and died. The formed blood elements were said to be within normal limits. Necropsy disclosed petechiae in all tissues, and a large subarachnoid hemorrhage in the brain. There were sarcoid granulomas in the lungs, lymph nodes, liver and spleen. These authors stated that since no cause could be found for the bleeding, it was probably of an allergic nature. They did not regard the sarcoidosis as related to the hemor-

rhages. Case 15 of Ricker and Clark's series was a 22 year old white male who died on the second hospital day of a massive pulmonary hemorrhage after an illness characterized by cough of one month's duration and a cold for four days. No laboratory studies were done. Necropsy revealed sarcoidosis of the lungs, lymph nodes, liver and spleen. No definite cause for the pulmonary hemorrhage could be ascertained, although the pathologist suggested that weakening of the pulmonary blood vessels by the perivascular granulomas might be a factor. Ricker and Clark further stated that the finding of sarcoidosis in the two cases with hemorrhage was purely coincidental and had no bearing on the development of the bleeding. In view of the analysis of the other cases presented above, we believe that the association of Boeck's sarcoid and hemorrhage is more than coincidental.

The following case is reported because of the rarity of hemorrhage during the course of sarcoidosis and because it is the first case, to our knowledge, in which massive gastrointestinal bleeding has occurred in association with the disease.

Case Report

The patient, a 50 year old white male, was admitted to the Beth-El Hospital on March 27, 1949, because of enlargement of his neck of one month's duration. The patient had a mild diabetes which was well controlled by diet. Examination disclosed enlarged discrete lymph nodes in the supraclavicular fossae on both sides of the neck and in the left axilla. The spleen was palpable two fingerbreadths below the left costal margin. The liver was slightly enlarged. Roentgenogram of the chest revealed enlargement of the mediastinal hilar lymph nodes. A biopsy of a cervical lymph node revealed the typical histologic features of Boeck's sarcoid. The serum total protein was 6.9 gm. per cent, with an albumin of 4.2 and a globulin of 2.7. The white blood count was 8,100, with 83 per cent hemoglobin and a normal differential count. Platelets were seen in normal amounts in the peripheral smear. The patient was discharged for further observation at home.

Four months later, after an asymptomatic interval, the patient was readmitted to the hospital because of vomiting of 2,000 c.c. of blood associated with vascular collapse. The patient was obviously in shock and was treated by numerous transfusions, totaling 12,000 c.c. during his three weeks' hospital stay. The admission hemoglobin was 23 per cent, but rose to 70 per cent after transfusions. The white blood count on admission was 22,000 and fell to normal limits within one week of admission. The serum total protein was 7.7 gm. per cent with albumin 4.0 gm. per cent and globulin 3.7 gm. per cent.

The patient continued to vomit as much as a liter of blood with large clots at one time, and had persistent melena. He would rally after transfusion but had repeated hematemeses. A platelet count done nine days after admission revealed 290,000 platelets per cu. mm. Because of the rapidly recurring bouts of hematemesis, an exploratory laparotomy was performed to exclude the possibility of a bleeding focus in the upper gastrointestinal tract. Careful inspection of the upper gastrointestinal tract was carried out, including a gastrotomy to inspect the interior of the stomach and proximal duodenum. The stomach and duodenum contained no blood, but the remainder of the small intestine was filled with blood. No ulcers or neoplasms were seen in the stomach, and the remainder of the gastrointestinal tract was said to be normal. Postoperatively, the patient developed a spiking fever as high as 107° F. and died on the seventh postoperative day. A bone marrow aspiration performed the day before showed an adequate number of megakaryocytes in the sternal marrow.

Necropsy Observations: Gross Description: The necropsy was performed four

and one-half hours after death. The body was that of a poorly nourished 50 year old white male. A few small cervical lymph nodes were felt. There was a recent 8 cm. right upper rectus abdominal incision. There were no effusions or fibrous adhesions in any of the serous cavities. The heart was of normal size, weighing 360 gm. No abnormalities were present in the valves, myocardium or coronary arteries. The lungs were slightly enlarged. Scattered over the visceral pleurae of both lungs were

FIG. 1. The spleen shows extensive generalized enlargement of the follicles and numerous confluent foci of sarcoid granuloma formation in the pulp.

numerous pinpoint to pinhead sized grayish nodules. The remainder of the lung parenchyma was vesicular, with the exception of the right lower lobe, which was granular, firm and friable. The spleen was markedly enlarged, weighing 700 gm. The capsule was smooth and gray. On section the red pulp was firm, and numerous grayish nodules, varying in size from 2 to 8 mm. in diameter, were found throughout the parenchyma (figure 1). No necrosis was seen in any of the nodules. The mucosa of the entire gastrointestinal tract was smooth and intact, with the

exception of a healing gastrotomy wound in the pyloric antrum. The small intestine from the ligament of Treitz to the cecum contained tarry material. No nodules, ulcerations or petechial hemorrhages were noted after careful examination. The pancreas was grossly unremarkable. The liver was moderately enlarged, weighing 2,100 gm. Except for slight congestion of the sinusoids, no remarkable changes were found. The gall-bladder wall was thin. The extrahepatic biliary ducts were patent. The adrenal glands showed no pathologic changes. The kidneys were slightly enlarged. The capsules stripped easily, leaving a smooth cortical surface marked by innumerable hemorrhages varying in size from 1 to 4 mm. in diameter (figure 2). The hemorrhages were limited to the cortical surfaces. The corticomedullary junctions were distinct in both kidneys. A few small mucosal hemorrhages were noted

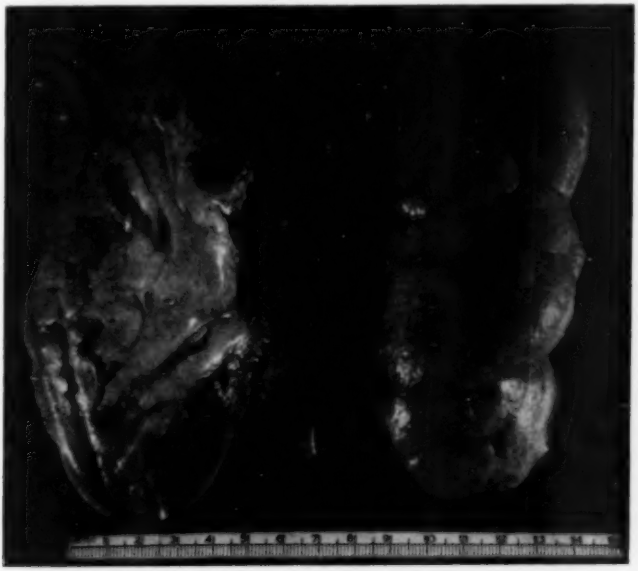

FIG. 2. There is extensive petechiasis of the external renal cortical surfaces and limited renal pelvic mucosal hemorrhage.

in the renal pelves. The bone marrow of the lumbar vertebrae was dark red in color and of the usual consistency. The brain was not examined. The lymph nodes in various sites were found to be enlarged. The most prominent enlargement was found in the mediastinal region, where a large chain of nodes, ranging in size from 0.4 to 2 cm., was noted (figure 3). These nodes were soft and uniformly gray on cut section, with numerous anthracotic markings visible throughout. Enlargement of lymph nodes was also seen in the cervical and periportal regions, especially surrounding the common bile duct.

Microscopic Examination: The aorta, heart, pancreas and adrenal glands showed no pathologic changes of note. In the lungs, numerous epithelioid tubercles were found beneath the visceral pleura and in diffuse distribution involving the interalveolar

septa (figure 4). Numerous Langhans-type giant cells and extensive fibrosis were noted in the pulmonary tubercles. Asteroid inclusions were present in the cytoplasm of many of the giant cells. No calcific inclusions of Schaumann were found. There was no caseation in any of the tubercles. In the spleen there was extensive involvement of both the red and white pulp by discrete and coalescent granulomas, characterized by the proliferation of epithelioid cells, multinucleated giant cells of the

FIG. 3. Mediastinal lymph nodes surrounding the tracheal bifurcation, the esophagus and the descending thoracic aorta are markedly enlarged. The nodes are discrete.

Langhans type, and occasional lymphocytes. Numerous intracytoplasmic asteroid inclusions were found in the splenic sections (figure 5). In the gastrointestinal tract no evidence of focal hemorrhage was found. No abnormal cellular infiltrations were noted in any portion of the gastrointestinal tract. In the liver, numerous fibrosing noncaseating tubercles were present in the portal triads. Except for focal hemorrhage in the Bowman's capsule spaces, no pathologic changes were found

in the kidneys. The lymph nodes showed extensive replacement of the normal landmarks by discrete and coalescent tubercles, which showed extensive fibrosis with the deposition of a hyaline material in the tubercles. Numerous megakaryocytes were found in the vertebral bone marrow. No abnormalities were seen in these cells.

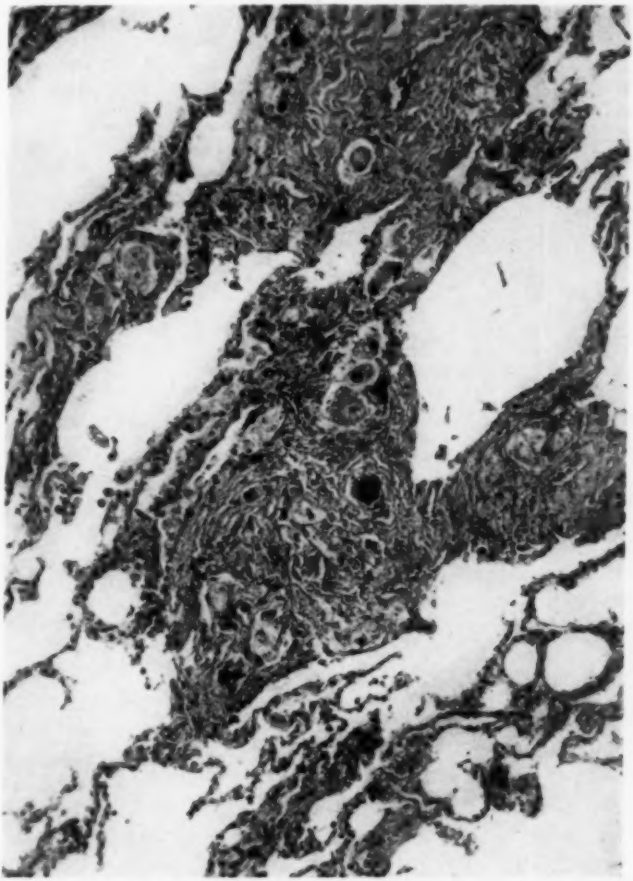

FIG. 4. The lungs are involved by numerous fibrosing interalveolar septal tubercles. Numerous asteroid inclusions are seen in the cytoplasm of the giant cells.

There was moderate hyperplasia of erythropoietic and myeloid elements of the marrow (figure 6). No lesions of sarcoidosis were found in the bone marrow.

Final Anatomic Diagnoses: Sarcoidosis involving spleen, lungs, liver, mediastinal and mesenteric lymph nodes; massive hemorrhage into the gastrointestinal tract, site of origin undetermined; petechiasis of kidneys; atelectasis and lobular pneu-

monia of the lower lobe of right lung; status postoperative exploratory laparotomy and gastrotomy.

Discussion

Within the past decade, the concept of hypersplenism has been popularized by the works of Dameshek,[8] Doan and Wright [5] and others. In general, these authors have contended that some toxic principle is elaborated in the diseased spleen which may either interfere with the liberation into the peripheral blood or cause increased destruction within reticuloendothelial cells of any one or all

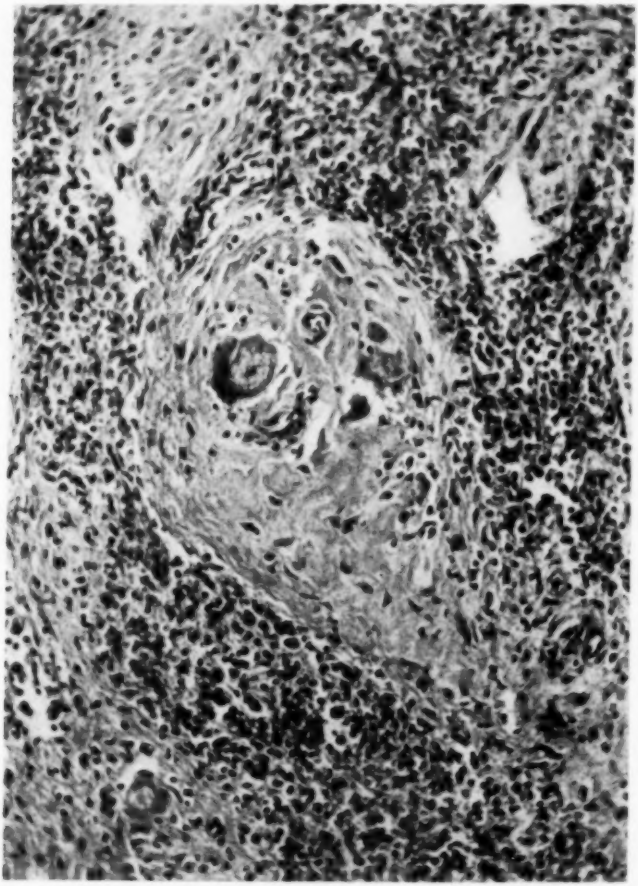

Fig. 5. Fibrosing epithelioid tubercles involve the splenic follicles. A large multinucleated giant cell contains a prominent intracytoplasmic asteroid inclusion.

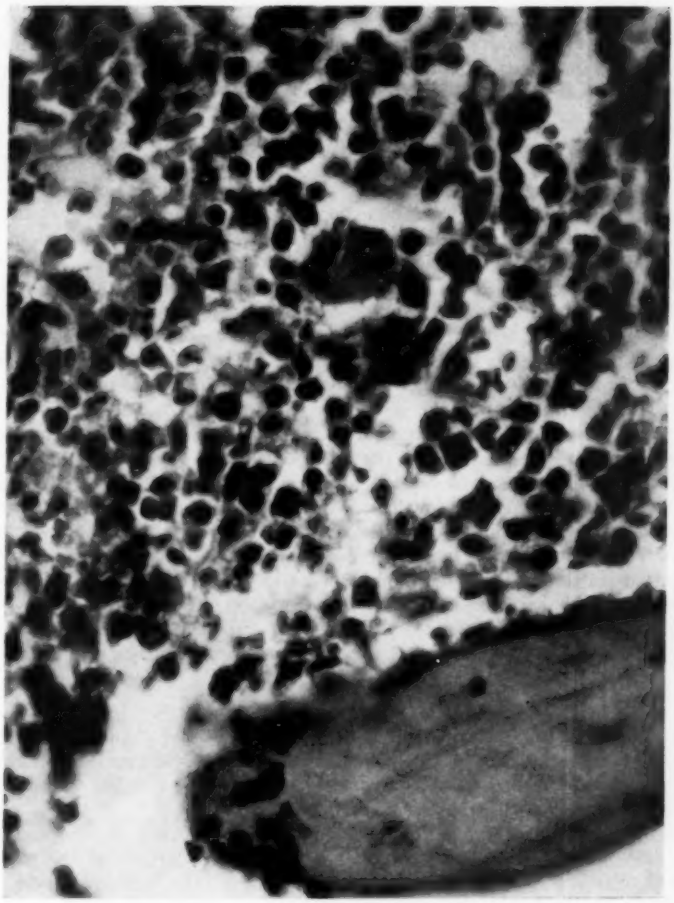

FIG. 6. The vertebral bone marrow shows hyperplasia of myeloid elements and a large megakaryocyte.

of the marrow elements. Thus, anemia, neutropenia or thrombocytopenia, or any combination of these effects, may result. It is emphasized that hypersplenism may occur as a primary disease of the spleen of as yet undetermined etiology, or may occur in the course of generalized systemic disorders, such as the lymphomas and Boeck's sarcoidosis, among others. It is significant that in all 10 cases demonstrating hemorrhagic episodes described in the literature, as well as in the case above recorded, the spleen was involved by the sarcoid granulomas.

Estimates of the frequency of involvement of the spleen in generalized sarcoidosis vary considerably, depending on whether clinical or necropsy investigations have been carried out. Thus, in the autopsy studies the incidence of splenic involvement has varied from 50 per cent [1] to 83 per cent.[7, 9] In the clinical series the incidence ranges from 25 per cent [10, 11] to 50 per cent.[12] One may assume from the above figures that the true incidence of splenic involvement in Boeck's sarcoid is approximately 50 per cent of all cases. This estimate makes more striking the significance of the universal involvement of the spleen in cases of Boeck's sarcoid exhibiting hemorrhagic manifestations.

The case under consideration is unique in that it is believed to be the first case of Boeck's sarcoid in which massive gastrointestinal hemorrhage has been observed. No gross lesions in the gastrointestinal tract could be found at necropsy to account for the bleeding. The extensive petechiasis of the kidneys reflects the purpuric tendency in our case. Although the platelet count on one occasion in the patient's second admission was 290,000 per cu. mm., the possibility of thrombocytopenia cannot be ruled out with this single observation. Of the 10 cases gathered from the literature, observations on platelet counts were made on seven occasions. In six of these there was a definite thrombocytopenia, while one showed a normal platelet count.

Although the number of cases of hemorrhage thus far observed during the course of Boeck's sarcoid is small, it is apparent that hemorrhage constitutes a rather grave complication of the disease. In view of the constant involvement of the spleen in cases of sarcoidosis associated with hemorrhagic states, it is suggested that serious consideration be given to the performance of splenectomy in patients with sarcoidosis when hemorrhage occurs without obvious cause. Furthermore, it should be noted that the cases reported by other authors who survived splenectomy showed no further hemorrhagic tendencies.[2, 3, 6]

Summary and Conclusions

1. A 59 year old male had sarcoidosis for at least five months. The initial stage was characterized by lymphadenopathy and splenomegaly. Repeated massive gastrointestinal hemorrhages were noted during the last month of life and did not respond to transfusion therapy.

2. Necropsy disclosed generalized sarcoidosis involving the spleen, lungs, liver and mediastinal and mesenteric lymph nodes. The site of the gastrointestinal bleeding was not discovered at necropsy. In addition, there were extensive petechial hemorrhages in the kidneys.

3. This case is presented as one of hypersplenism caused by sarcoidosis involving the spleen, with probable resultant thrombocytopenia and extensive hemorrhagic manifestations.

4. On the basis of the present and other reported cases in the literature, it is suggested that when otherwise unexplained hemorrhage occurs during the course of Boeck's sarcoid serious consideration be given to the performance of splenectomy.

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EDITORIAL

BACTERIAL VERSATILITY

THE marvellous adaptability of living creatures has long excited the awe and wonder of the natural philosopher; recently it has stirred less reverent thoughts in the minds of modern therapists.

A few years ago in these columns attention was drawn to the appearance of bacterial resistance.[1] Since that time we have encountered numerous variations on the resistance theme, and, what is more significant, we have learned that "resistance" is only the bottom rung of bacterial evasion. The disturbing situation has been excellently reviewed by Garrod in a recent lecture and published article.[2]

Since Ehrlich led the way it has been frequently pointed out that micro-organisms can accustom themselves to a variety of antiseptics. Resistance did not assume widespread and practical importance, however, until the sulfonamides crossed swords with the gonococcus. This organism almost immediately demonstrated its refractory capabilities which have been repeatedly observed since, and the percentage of treatment failures has progressively increased until it appeared to reach a climax of 85.8 per cent in 1949.[3] The pneumococcus and hemolytic streptococcus have shown a less marked tendency to develop resistance to the sulfonamides, while it is indeed fortunate that the meningococcus has so far shown no conclusive sign of habituation.

Resistance to penicillin has shown an analogous pattern. Again the phenomenon has appeared predominantly in one bacterial species; and again the development of resistance is, sometimes at least, the result of a drug-inhibitor produced by the organism. In the realm of penicillin the organism is, of course, the staphylococcus, and the inhibiting enzyme produced is penicillinase. Although gonococci and meningococci can be made resistant in vitro,[4, 5] as can pneumococci[6, 7] and hemolytic streptococci of Groups B and C,[8] none of these appear to develop significant resistance in the treated patient. We are particularly fortunate that Group A streptococci

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and the *Treponema pallidum* have so far shown no signs of becoming penicillin-resistant.

It has, however, been observed on several occasions that some organisms become increasingly resistant in the body in the course of unsuccessful treatment. Examples of this have been put on record notably in cases of subacute streptococcal endocarditis,[9, 2] staphylococcal endocarditis,[9, 10] and actinomycosis.[2]

It may be well to reëmphasize that resistant strains may emerge as a result of two distinct processes: an originally resistant strain may become predominant as its susceptible relatives are liquidated (selection), or the individual organism may become acclimatized to its hostile environment and learn to tolerate it (adaptation, habituation, acquired resistance). While both the gonococcus and the staphylococcus are capable of adapting and acquiring resistance, it is thought that in each case selection is the chief mechanism which has led to the current prevalence of refractory organisms.

Against streptomycin the pattern of resistance differs. It appears that not only are all species of bacteria capable of developing resistance to the antibiotic, but this can occur with unusual rapidity; indeed resistant organisms have been recovered after only one day's treatment.[11, 12, 2]

In the use of chloramphenicol, aureomycin and terramycin, resistance has not yet reared its ugly head significantly high. It has occurred, however, contrary to the tenor of early optimistic prophecies. It has been observed in clinical staphylococcal infections during treatment with aureomycin,[13, 14, 10] and Gram-negative infectors of the urinary tract have developed resistance to chloramphenicol.[2] A number of other organisms have been reported to develop resistance to aureomycin both in vitro (e.g., *Streptococcus fecalis, E. coli*), and in vivo (e.g., *Aerobacter aerogenes, Klebsiella pneumoniae*, streptococci of Groups A and C, and alpha hemolytic streptococci).

Herrell and his colleagues have recently investigated strains of various organisms made resistant to aureomycin, chloramphenicol, terramycin, and streptomycin.[15] They determined that strains of *E. coli* and *Aerobacter*

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aerogenes made resistant to terramycin, regularly had increased resistance to aureomycin and chloramphenicol, but not to streptomycin. This and further experiments suggest that terramycin shares a common denominator of resistance with aureomycin and chloramphenicol, but that the pattern of streptomycin-resistance is unique. Bryson and Demerec,[16] indeed, divide resistance into two types—the streptomycin type in which complete resistance may be brought about by a single genetic change, and the penicillin type in which complete resistance requires a series of multiple genetic steps. From their experiments these authors concluded that aureomycin-, chloramphenicol-, terramycin-, and neomycin-resistance were all of the penicillin type.

Resistance to bacitracin in vitro has been induced in streptococci of Groups A, B and C,[17] and in *Staphylococcus aureus*.[18] To aerosporin (polymyxin B) resistance has proved particularly difficult to cultivate, though some degree of resistance on the part of *S. typhi* has been produced in vitro and remained operative in vivo when mice were infected with the resistant strain.[19] A strain each of *Ps. aeruginosa* and *Aerobacter aerogenes* have shown the capacity for developing considerable resistance in vitro.[20]

When the resistant bacterium goes a stage further, it actually requires yesterday's poison for its continued existence. Such "dependence" has been contrived by a number of cunning species. In the laboratory meningococci,[21] *Mycobacterium tuberculosis*,[22] *E. coli*, Pseudomonas and others [23, 24, 25] have all shown themselves capable of developing dependence on streptomycin, and a strain of Friedlander's bacillus has been made dependent for growth on chloramphenicol.[26]

Even more important than dependence—because of its potentially greater seriousness—is the phenomenon of bacterial stimulation. It is surely the

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[19] Brownlee, G., and Bushby, S. R. M.: Chemotherapy and pharmacology of aerosporin: a selective Gram-negative antibiotic, Lancet **1**: 127, 1948.

[20] Jawetz, E., and Coleman, V. R.: Laboratory and clinical observations on aerosporin (polymyxin B), J. Lab. and Clin. Med. **34**: 751, 1949.

[21] Miller, C. P., and Bohnhoff, M.: Two streptomycin-resistant variants of meningococcus, J. Bact. **54**: 467, 1947.

[22] Lenert, T. F., and Hobby, G. L.: Letter to editor, Streptomycin-dependent strains of *Mycobacterium tuberculosis*, Am. Rev. Tuberc. **59**: 219, 1949.

[23] Rake, G.: Streptomycin as essential nutrilite, Proc. Soc. Exper. Biol. and Med. **67**: 249, 1948.

[24] Paine, T. F., and Finland, M.: Streptomycin-sensitive, -dependent and -resistant organisms, Science **107**: 143, 1948.

[25] Kushnick, T., Randles, C. I., Gray, C. T., and Birkeland, J. M.: Variants of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* requiring streptomycin, Science **106**: 587, 1947.

[26] Gocke, T. M., and Finland, M.: Development of chloramphenicol-resistant and chloramphenicol-dependent variants of a strain of *Klebsiella pneumoniae*, Proc. Soc. Exper. Biol. and Med. **74**: 824, 1950.

master stroke of bacterial subtlety when the organism, instead of being suppressed, is actually stimulated to more vigorous growth by what was once a lethal chemical. There is evidence that this results from exposure to sublethal levels of the drug, and may therefore simply be an expression of the Arndt-Schultze law which states that poisons in small doses are stimulants. Since the formulation of this law in 1888 it has been repeatedly observed that low concentrations of many bacterial antagonists actually accelerate bacterial growth. It is disturbing, to say the least, to find that our priceless antibiotics can behave similarly.

The evidence so far accumulated concerns mainly penicillin. As long ago as 1945 it was demonstrated in vitro, by the agar diffusion technic, that a zone of enhanced growth could be obtained.[1] This suggested that a critical concentration of the diffusing penicillin actually stimulated the growing organism. The phenomenon has been repeatedly observed by other workers.

Curran and Evans [27] found that low concentrations of either penicillin or streptomycin could accelerate the growth of streptococci and staphylococci in a skim-milk medium, and Miller and his colleagues [28] showed that the growth of *Staphylococcus aureus* in broth was maximally enhanced by a concentration of penicillin only about one-fifth of that required to inhibit its growth completely.

Garrod [2] has conclusively shown that appropriate concentrations of penicillin can stimulate the growth of both penicillin-sensitive and penicillin-resistant organisms. He found, for instance, that 0.004 unit per c.c. accelerated staphylococcal growth, while *Pseudomonas pyocyanea* was stimulated by 4 units per c.c. Interestingly he found that such stimulation was enhanced by three factors which in themselves are unfavorable to bacterial growth. Thus penicillin particularly stimulated the growth of relatively dormant cells from older cultures. Again, the poorer the medium the greater was the stimulating effect of penicillin. And thirdly stimulation was more pronounced when the culture was maintained at a few degrees below 37° C.

In experimental animals a few instances of suspected stimulation have been reported. It was found that penicillin increased the mortality in mice infected with *Salmonella typhi*,[29] and also increased the death rate of chick embryos inoculated with *Candida albicans*.[30]

Clinically a number of bacterial turncoats have been encountered. They have appeared for the most part as "superinfections" during antibiotic ther-

[27] Curran, H. R., and Evans, F. R.: Stimulation of sporogenic and nonsporogenic bacteria by traces of penicillin or streptomycin, Proc. Soc. Exper. Biol. and Med. **64**: 231, 1947.

[28] Miller, W. S., Green, C. A., and Kitchen, H.: Biphasic action of penicillin and other sulphonamide similarity, Nature **155**: 210, 1945.

[29] Randall, W. A., Price, C. W., and Welch, H.: Demonstration of hormesis (increase in fatality rate) by penicillin, Am. J. Pub. Health **37**: 421, 1947.

[30] Foley, G. E., and Winter, W. D.: Increased mortality following penicillin therapy of chick embryos infected with *Candida albicans* var. *stellatoidea*, J. Infect. Dis. **85**: 268, 1949.

apy—that is to say, while the sensitive organism is being eliminated by the drug, a resistant bacterium appears to take its place. Coliform bacilli have replaced the normal flora of the mouth and throat during local treatment with penicillin,[31] moniliasis has followed the exhibition of penicillin, aureomycin and chloramphenicol,[32, 33] and during the treatment of pneumonia Gram-negative organisms have appeared to assume the role of substituted pathogens.[34, 35] Numerous other investigators have noted "drastic dislocations" of bacterial flora.[36, 37, 38]

At times it is impossible to be certain that such organisms are not merely filling the gap left by the death of sensitive species. It may be remembered that one of the first practical uses to which penicillin was put by its discoverer in its earliest preclinical days, was the isolation of *Hemophilus influenzae* in the laboratory from sputums and throat cultures.[39] It was quite clear that the penicillin applied in the culture plate simply killed off susceptible inhabitants of the sputum, leaving the resistant Hemophilus to flourish. Without the aid of penicillin the defenceless Hemophilus was almost invariably overgrown by sturdier cocci.

It is highly probable that such mere substitutions can occur in the body. Moreover it seems not unlikely that they can occur without the substituted organism representing a true pathogenic infection. One not infrequently observes a patient treated for pneumococcal pneumonia whose sputum, after a few days of penicillin therapy, grows a pure culture of *Hemophilus influenzae*. The patient's clinical progress is meanwhile uninterrupted, and it seems most likely that we are in such instances witnessing in vivo an extension of Fleming's in vitro observation.

On the other hand the substituted organism is sometimes enabled to multiply and invade. In one of Weinstein's cases, for example, after a few days' treatment of pneumonia with penicillin, *H. influenzae* took over and caused a secondary pneumonia and septicemia.[34]

But suppression with substitution is not the whole story, for it cannot explain all "superinfections." Garrod [2] observed three cases of endocarditis

[31] Long, D. A.: Effect of penicillin on bacterial flora of mouth, Brit. M. J. **2**: 819, 1947.
[32] Woods, J. W., Manning, I. H., and Patterson, C. N.: Monilial infections complicating the therapeutic use of antibiotics, J. A. M. A. **145**: 207, 1951.
[33] Harris, H. J.: Aureomycin and chloramphenicol in brucellosis, with special reference to side effects, J. A. M. A. **142**: 161, 1950.
[34] Weinstein, L.: The spontaneous occurrence of new bacterial infections during the course of treatment with streptomycin or penicillin, Am. J. M. Sc. **214**: 56, 1947.
[35] Appelbaum, E., and Leff, W. A.: Occurrence of superinfections during antibiotic therapy, J. A. M. A. **138**: 119, 1948.
[36] Meads, M., Rowe, W. P., and Haslam, N. M.: Alterations in the bacterial flora of the throat during oral therapy with aureomycin, Arch. Int. Med. **87**: 533, 1951.
[37] Lipman, M. O., Coss, J. A., Jr., and Boots, R. N.: Changes in bacterial flora of the throat and intestinal tract during prolonged oral administration of penicillin, Am. J. Med. **4**: 702, 1948.
[38] Smith, J. W., and Bloomfield, A. L.: The effect of penicillin on the aerobic bacterial flora of the normal throat, Stanford M. Bull. **6**: 469, 1948.
[39] Fleming, A.: On the antibacterial action of cultures of a Penicillium, with special reference to their use in the isolation of *B. influenzae*, Brit. J. Exper. Path. **10**: 226, 1929.

treated with penicillin who developed urinary infections with *Pseudomonas pyocyanea* during the course of treatment, "for no apparent reason other than the presence of the drug in the urine." Another patient being treated for actinomycosis developed an overwhelming Pseudomonas pyemia.[40] Such examples represent the appearance of invaders where presumably none previously existed, and are not therefore mere substitutions. Garrod also mentions a patient with a staphylococcal lung abscess (and with no tubercle bacilli in his sputum) who died a month after penicillin therapy was instituted from fulminating pulmonary tuberculosis; and he records—what he is careful to state is only an impression based on a number of similar cases studied—that during treatment with penicillin for some other condition, a previously unrecognized or relatively quiescent tuberculous focus may become active.

It cannot be asserted that any such clinical experiences offer proof that bacterial stimulation by antibiotics occurs in the human body. They are suggestive, however, and weight is lent to the assumption by the clear demonstration that antibiotics can act as bacterial stimulants in vitro. While it is not good science to accept probabilities as facts, it is frequently good sense to treat them with respect. It would be wrong to regard the prevalence of bacterial stimulation as established, but it would be more foolish to turn our backs on what appears to be reasonably legible writing on the antibiotic wall.

The situation cannot be better summarized than in Garrod's own concluding words.[2] Bacteria "are not taking the present widespread attack on them lying down: some are defending themselves very effectively, and some are even turning our weapons to their own advantage. So far the supply of new antibiotics has more than matched the capacity of bacteria to resist them, but if this supply should cease—and presumably the number yet to be discovered is limited—the time may come when a few of the more enterprising species will flourish more or less unhindered."

The chemotherapeutic struggle has been further complicated by another embarrassing phenomenon, "antibiotic antagonism." Much has already been written on this subject and on the inseparable subject of combined antibiotic therapy, and they will receive only brief and incomplete consideration here.

It has been shown that one antibiotic can interfere with another's action. Thus it has been demonstrated that chloramphenicol interferes with the action of penicillin both in the test tube and in experimental infections in mice.[41]

It is not difficult to rationalize this antagonism, for it is known that

[40] Christie, R. V., and Garrod, L. P.: A review of the work of a penicillin therapeutic research unit, Brit. M. J. **1**: 513, 1944.

[41] Jawetz, E., Gunnison, J. B., Speck, R. S., and Coleman, V. R.: Studies on antibiotic synergism and antagonism. The interference of chloramphenicol with the action of penicillin, Arch. Int. Med. **87**: 349, 1951.

penicillin is bactericidal and probably acts mainly on actively multiplying organisms. Chloramphenicol, on the other hand, is bacteriostatic, and therefore suppresses the organism preventing its active multiplication. If the two antibiotics are applied simultaneously penicillin is denied optimal conditions for action, and becomes a much less effective bacterial killer. It should be added that no clear-cut evidence has yet been adduced that such interference operates in the treatment of clinical infections.

Aureomycin and terramycin are also suppressive in their action, whereas streptomycin in high concentrations is mainly bactericidal for slowly multiplying and resting forms. As it is well known that most infecting bacterial populations contain both rapidly and slowly multiplying members, it is entirely logical to administer penicillin and streptomycin simultaneously. And indeed this combination has been shown to be clinically effective in a disease—enterococcal endocarditis—where each drug individually has been found wanting.[42] It is the considered opinion of some authorities that in the light of present knowledge the combination of penicillin with streptomycin is the only legitimate form of dual antibiotic therapy.[43]

The subtleties of bacterial evasion, together with the recognition of antagonism between the antibiotics themselves, underscore the need for wisdom in the selection and application of these drugs. The realities of the situation should not escape us in our therapeutic complacency, and should be a warning not to squander our antibiotic fortune at the present prodigal rate. It has been stated often, but it apparently cannot be emphasized enough, that these valuable drugs should not be hurled at the heads of each and every unidentified infection.

H. J. L. M.

[42] Robbins, W. C., and Tompsett, R.: Treatment of enterococcal endocarditis and bacteremia. Results of combined therapy with penicillin and streptomycin, Am. J. Med. **10**: 278, 1951.

[43] Woodward, T. E.: Personal communication.

REVIEWS

Spatial Vector Electrocardiography: Clinical Electrocardiographic Interpretation. By ROBERT P. GRANT, M.D., National Heart Institute, Bethesda, Md., and E. HARVEY ESTES, JR., M.D., U. S. Naval Hospital, Bethesda, Md. 149 pages; 14 × 21.5 cm. The Blakiston Company, Philadelphia. 1951. Price, $4.50.

The authors' object in this volume is to indicate how vector principles can be used in the clinical interpretation of the electrocardiogram. They stress the "vector method of interpretation," using the conventional electrocardiographic electrode positions, and believe this method should supplement rather than supplant other methods of interpretation. The authors' method, essentially, is to construct frontal plane QRS and T vectors from the routine extremity leads, and to locate these vectors in space by the use of the conventional precordial leads. The resultant is termed the mean spatial QRS and T vector respectively. They then discuss the clinical application of the "spatial vector method," relying chiefly upon variations in the positions of the mean spatial QRS and T vectors and their relationship to each other.

The method presented for deriving the mean spatial vectors has never been shown to be reliable. Derivation of the vectorcardiogram from routine precordial leads (the method here used) is by no means accurate, for the precordial leads do not all lie on the same plane, and the "transitional zone" is frequently difficult or impossible to identify. It has been shown, by actually recorded vectorcardiograms, that similar series of precordial leads V-1 to V-6 may represent totally different horizontal vector loops, as in right bundle branch block and right ventricular hypertrophy. There are no actual recorded vectorcardiograms in this volume. That actual rather than inferential vectors are needed is shown by the discussion of the differential diagnosis between left bundle branch block and left ventricular hypertrophy (p. 73), and by publications of others on this subject.

The text is at times contradictory, and the reasoning frequently circuitous. There is a limited bibliography of 13 references, and no directly indicated references. It is not stated whether actual loops ever have been obtained to support the theoretical concepts presented. The authors' comment on the section on abnormalities of the T vector may well apply to other sections: ". . . although the material has been presented rather dogmatically and with appearance of definiteness, it is actually based largely upon tentative formulations and partially proved hypotheses."

The authors are to be congratulated upon popularizing certain vector concepts. It is to be regretted that they reduce vectorcardiography to a method of interpreting routinely recorded conventional electrocardiograms; i.e., vector analysis. There is good reason to believe that vectorcardiography offers information over and above that which can be obtained from conventional electrocardiography, whether interpreted directly, or indirectly by "vector analysis."

S. S.

Growth and Development of Children. By ERNEST H. WATSON, M.D., and GEORGE H. LOWREY, M.D. 260 pages; 15 × 23.5 cm. The Year Book Publishers, Inc., Chicago. 1951. Price, $5.75.

This is a long awaited volume which presents in well-organized style the complete factual material of a subject which previously has been presented in a segmental manner.

The material is presented in a logical sequence. A brief discussion of heredity followed by an outline of environmental factors precedes discussion of fetal growth

and development. These early chapters are followed by full discussion of all aspects of post-natal growth; the book concludes with a chapter on abnormal growth.

The subject matter is presented clearly. Summary of material is placed at the end of each chapter and provides a valuable review for the reader. The bibliography is adequate and utilizes the most modern articles. Foreign literature is rarely cited, except for articles which appear in English.

The volume is recommended for physicians and workers who desire a comprehensive review of the subject of growth and development in children.

J. E. B.

An Atlas of Normal Radiographic Anatomy. By ISADORE MESCHAN, M.A., M.D., Professor and Head of the Department of Radiology, University of Arkansas School of Medicine, with the assistance of R. M. F. FARRER-MESCHAN, M.B., B.S. (Melbourne, Australia). 593 pages; 17 × 26 cm. W. B. Saunders Company, Philadelphia. 1951. Price, $15.00.

This atlas is an excellent treatise written so that students, residents and physicians in general may obtain a basic knowledge of normal radiographic anatomy. The authors, in a clear, concise manner, have succeeded in presenting: (1) basic morbid anatomy as it is applicable to radiography; (2) the manner in which routine radiographic views are obtained; (3) a concept of the film so obtained; (4) the anatomic parts best visualized on these views; (5) changes in the growth and development, and (6) some of the more common variations of normal.

The first part of each chapter is devoted to a gross anatomical discussion, followed by a description of the various views which can be employed to bring out essential features of that particular anatomical structure. The description of each view is augmented by a sketch to illustrate proper positioning, the roentgenogram obtained, and a labelled sketch of this roentgenogram.

The text is well written for easy, understandable reading and contains a wealth of fine drawings and roentgenograms to illustrate the important anatomical structures. This book is an excellent adjunct to the library of radiologists and other physicians who desire a more thorough knowledge of normal radiographic anatomy.

J. M. D.

Cunningham's Text-Book of Anatomy. 9th Ed. Edited by JAMES C. BRASH, M.C., M.A., M.D., D.Sc., F.R.C.S. Ed., F.R.S.E., Professor of Anatomy, University of Edinburgh. 1604 pages; 16.5 × 26 cm. Oxford University Press, New York. 1951. Price, $14.00.

The revised ninth edition of this standard text of human anatomy follows, essentially, the general pattern of previous editions. Contributors to the sections on Osteology, Arthrology and Surface and Surgical Anatomy have been changed from those listed in the eighth edition. In conformity with the present trend the Anglicized version of anatomical terms is used throughout the book, except in a few instances where the Latinized form may help the student to appreciate the derivation of related words. The series of radiographic plates featured in the various sections of the book are excellent, especially those found in the section on the blood-vascular system. These plates appear in positive reproduction and show the arteries of the elbow, hand, knee and foot regions injected with radiopaque material. They should prove particularly helpful to the student in depicting certain features of anatomy often difficult to display by the usual methods of dissection.

New illustrations related to early human development and external form of the embryo have been incorporated in the section on Embryology. The material in the

section on Surface and Surgical Anatomy is arranged on a regional basis as opposed to the systematic arrangement in the main body of the text. This section has been enlarged and several useful tables on the segmental innervation of the limbs have been added. In the appendix to this section certain fundamental principles and procedures used in radiography are elucidated. The entire section should prove exceedingly interesting and profitable to the beginning student in anatomy.

It is stated in the preface that: "The most important innovation of this edition of the text-book is the provision of a list of references at the end of each section. . . . Classical references have not been omitted; but in general the several contributors, by including recent scientific papers and monographs, have endeavoured to indicate the sources which themselves provide more complete bibliographies." Generally the references are well chosen, although no recent publications on the anatomy of the pelvic and perineal fascias are included.

This book is recommended as a text-book for students in anatomy and as a reference book for other workers in the biological sciences.

W. E. H.

The Genealogy of Gynaecology. 2nd Ed. By JAMES V. RICCI, A.B., M.D. 494 pages; 18 × 27 cm. The Blakiston Company, Philadelphia. 1950. Price, $8.50.

From the facile pen of this eminent gynecologist-historian comes an enlarged and revised second edition of a work which has become classic in its field. The author's broad perspective in presenting scattered facts of history from 2000 B.C., to 1800 A.D., is evident against the background of general medical history and its accepted epochal divisions. The tremendous amount of material presented is illuminated by direct quotation, and innumerable footnotes and bibliographies, together with biographical notes of the authors quoted. Obstetrical history is interwoven. The book is attractively bound and clearly printed. There is an index of personal names. A subject index would have been helpful and would have made the book more generally useful for reference. The work is highly recommended to all those interested in the history of gynecology and obstetrics.

J. E. S.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annual Report on Stress. By HANS SELYE, M.D., Ph.D. (Prague), D.Sc. (McGill), F.R.S. (Canada), Professor and Director of the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal. 644 pages; 25 × 17 cm. 1951. Acta, Inc., Montreal, Canada. Price, $10, plus 34¢ mailing charges if ordered from publisher.

The Approach to Cardiology. By CRIGHTON BRAMWELL, M.A., M.D., F.R.C.P., Professor of Cardiology in the University of Manchester, etc.; with a Foreword by A. V. HILL, C.H., O.B.E., Sc.D., F.R.S., Foulerton Research Professor of the Royal Society. 122 pages; 25.5 × 15.5 cm. 1951. Oxford University Press, New York. Price, $3.75.

Biological Antagonism: The Theory of Biological Relativity. By GUSTAV J. MARTIN, Sc.D., Research Director, The National Drug Company, Philadelphia. 516 pages; 23.5 × 15.5 cm. 1951. The Blakiston Company, Philadelphia. Price, $8.50.

Clinical Allergy: A Practical Guide to Diagnosis and Treatment. 2nd Ed. By SAMUEL J. TAUB, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Allergic Diseases, the Chicago Medical School, etc. 276 pages; 24.5 × 16 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $4.50.

Conteben bei Lungentuberkulose. By H. KLEESATTEL and W GÜRICH. 154 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 22.50.

Deficiency Diseases in Japanese Prison Camps—Medical Research Council Special Report Series No. 274. By DEAN A. SMITH and MICHAEL F. A. WOODRUFF; with an Introduction by J. BENNET. 213 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 6s. 6d. net.

Diagnosis and Treatment of Menstrual Disorders and Sterility. 3d Ed. By CHARLES MAZER, M.D., F.A.C.S., Formerly Associate Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc.; and S. LEON ISRAEL, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc. 583 pages; 24 × 16 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

Expert Committee on Mental Health: Report on the First Session of the Alcoholism Subcommittee, Geneva, 11–16 December 1950—World Health Organization Technical Report Series No. 42. 24 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva; Agent in U.S.A.: Columbia University Press, International Documents Service, 2960 Broadway, New York. Price, 15¢.

Die Gesunde und Kranke Wirbelsäule in Röntgenbild und Klinik. By GEORG SCHMORL and HERBERT JUNGHANNS. 281 pages; 29 × 20.5 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 69.–.

Histologie und mikroskopische Anatomie des Menschen. By W. BARGMANN. 210 pages; 26.5 × 18 cm. 1948. Georg Thieme Verlag, Stuttgart. Price, geb. DM 19.60.

Histologie und mikroskopische Anatomie des Menschen. By W. BARGMANN. 563 pages; 26.5 × 18 cm. 1951. Georg Thieme Verlag, Stuttgart. Price, Ganzleinen DM 45.–.

Kymographische Röntgendiagnostik zur Beurteilung des Herzens in Beispielen. By PLEIKART STUMPF. 120 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 25.50.

Liver Disease—A Ciba Foundation Symposium. Consulting Editor: SHEILA SHERLOCK, M.D., F.R.C.P.; Editor for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch. 249 pages; 21 × 14 cm. The Blakiston Company, Philadelphia. Price, $5.00.

Physical Medicine and Rehabilitation for the Clinician. Edited by FRANK H. KRUSEN, M.D. 371 pages; 25.5 × 16.5 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $6.50.

The Rockefeller Foundation Directory of Fellowship Awards for the Years 1917–1950. With an Introduction by CHESTER I. BARNARD, President of the Foundation. 296 pages; 26 × 19.5 cm. 1951. The Rockefeller Foundation, New York. Distributed free of charge to interested institutions or individuals.

The Scottish Chemist's Index of Modern Remedies, 1951—First North American Edition. 115 pages; 24.5 × 18.5 cm. (paper-bound). 1950. The Scottish Chemist, Box 275, Terminal A, Toronto, Canada. Price, 1 copy, $2.00; 3 copies, $5.50; 6 copies, $10.75; 12 copies, $20.00—all post free.

The Specialties in General Practice. Edited by RUSSELL L. CECIL, M.D., Professor of Clinical Medicine, Emeritus, Cornell University Medical College, New York City. 818 pages; 26.5 × 18 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $14.50.

Surgical Practice of the Lahey Clinic. By MEMBERS OF THE STAFF OF LAHEY CLINIC, BOSTON. 1,014 pages; 25.5 × 17 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $15.00.

Textbook of Refraction. By EDWIN FORBES TAIT, M.D., Ph.D., Associate Professor of Ophthalmology, Temple University School of Medicine, etc. 418 pages; 25.5 × 16.5 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $8.00.

Topographische Ausdeutung der Bronchien im Röntgenbild. By CLAUS ESSER. 152 pages; 31 × 21.5 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 33.–.

You Can Too! By MARY JANE MOORE, R.N. Illustrated by KATHLEEN HAMMOND. 142 pages; 27.5 × 22 cm. (paper-bound, loose-leaf). 1950. The J. J. Tepper Corporation, New York. Price, $2.00.

Your Diabetes: A Complete Manual for Patients. 2nd Ed. By HERBERT POLLACK, M.D., Associate Physician for Metabolic Diseases, Mount Sinai Hospital, New York; and MARIE V. KRAUSE, M.S., Consulting Dietician. 212 pages; 21 × 14 cm. 1951. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.00.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. John R. Spannuth, Reading, Pa.
Dr. James H. Townsend, Buffalo, N. Y.
Dr. W. Gordon Hartnett, Fosteria, Ohio
Dr. Michael A. Cogan, Springfield, Mass.

A.C.P. Postgraduate Courses, Spring of 1952

Consult the Advertising Section, page 54, for full outline of Postgraduate Courses offered by the American College of Physicians from January to June, 1952. A Preliminary Postgraduate Bulletin has been published and distributed to all members of the College and to non-members on the mailing list. A Final Postgraduate Bulletin, which gives the full faculties and outlines of courses, is in course of publication.

The following full details concerning Course No. 2, Current Concepts of Allergy and Associated Disorders, being available, are published herein in advance.

COURSE NO. 2

CURRENT CONCEPTS OF ALLERGY AND ASSOCIATED DISORDERS

(March 3–7, 1952)

Washington University School of Medicine
St. Louis, Mo.

Harry L. Alexander, M.D., F.A.C.P., *Director*

(Minimal Registration, 25;
Maximal Registration, 50)

Fees: A.C.P. Members, $30.00
Non-members, $60.00

Officers of Instruction

(All members of the faculty are from Washington University School of Medicine unless otherwise indicated.)

Harry L. Alexander, M.D., F.A.C.P., Professor of Clinical Medicine.
Samuel C. Bukantz, M.D., Assistant Professor of Medicine.
Merrill W. Chase, Ph.D., Associate, Rockefeller Institute for Medical Research, New York, N. Y.
Leo H. Criep, M.D., F.A.C.P., Associate Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pa.
Gustave Dammin, M.D., Professor and Head of the Department of Pathology.
William H. Daughaday, M.D., Assistant Professor of Medicine.
Douglas Eastwood, M.D., Assistant Professor of Anesthesiology.

CHARLES H. EYERMANN, M.D., Assistant Professor of Clinical Medicine.
EDWIN F. GILDEA, M.D., Professor and Head of the Department of Neuropsychiatry.
ROBERT J. GLASER, M.D., Assistant Professor of Medicine.
STANLEY F. HAMPTON, M.D., Instructor in Clinical Medicine.
CARL G. HARFORD, M.D., Associate Professor of Medicine.
WILLIAM J. HARRINGTON, M.D., Instructor in Medicine.
MARY C. JOHNSON, A.B., Research Assistant in Medicine.
CARL V. MOORE, M.D., F.A.C.P., Professor of Medicine.
JOSEPH W. NOAH, M.D., Instructor in Clinical Medicine.
ADOLPH ROSTENBERG, JR., M.D., Associate Professor of Dermatology, University of Illinois College of Medicine, Chicago, Ill.
KEITH S. WILSON, M.D., Assistant Professor of Clinical Medicine.
W. BARRY WOOD, JR., M.D., F.A.C.P., Professor and Head of the Department of Medicine.

This course is designed primarily for those interested in the broad aspects of human hypersensitiveness according to present thought. It will include a wide variety of disorders, resulting from antigen-antibody reactions, which, instead of conferring protection induce many clinical syndromes. This immune mechanism underlies bronchial asthma, the allergic aspect of infectious diseases, drug hypersensitiveness, serum sickness, transfusion reactions and other hematological abnormalities. The relation of allergy to collagen diseases, as periarteritis nodosa and others that respond to ACTH, will be considered. Although emphasis will be placed on clinical aspects, underlying mechanisms will be elaborated.

Hotel Accommodations: Hotel Kings-Way, St. Louis 8, Mo., Mr. Harvey D. Brown, Manager. Single rooms with bath, $3.50; twin-bedded rooms with bath, $6.00. Make application direct, identifying yourself with the American College of Physicians and this course.

Meeting Place: Most of the sessions of the course will be held in the Elliott Auditorium of the McMillan Hospital, which is attached to the Barnes Hospital, 600 South Kingshighway. All registrants for this course should report at the Information Desk, McMillan Hospital, for directions.

OUTLINE OF COURSE

Monday, March 3

A.M. Session

8:30– 9:00 Registration.

THE ASTHMA-HAY FEVER GROUP

9:00–10:00 Immunological Considerations.
Dr. Bukantz.

10:00–11:00 The Mechanism of Bronchial Asthma.
Dr. Alexander.

11:00–12:00 Allergic and Non-allergic Asthma.
Dr. Hampton.

12:00– 1:00 Pulmonary Emphysema and Cor Pulmonale.
Dr. Wood.

P.M. Session

2:00– 3:00 Hay Fever Problems.
Dr. Eyermann.

3:00– 4:00 Morphologic Anatomy of Asthma and Its Complications.
Dr. Dammin.

4:00– 5:00 Discussion.
8:00 Round Table: Allergic Vasomotor Rhinitis, Headache and Gastrointestinal Disturbances.
Drs. Alexander, Bukantz, Eyermann, Hampton, Noah and Wilson.

Tuesday, March 4

A.M. Session

ALLERGY TO INFECTIOUS AGENTS

9:00–10:00 Clinical Significance of Allergy in Bacterial and Virus Diseases.
Dr. Harford.
10:00–11:00 The Rôle of Allergy in Rheumatic Fever and Other Streptococcal Infections.
Dr. Glaser.
11:00–12:00 The Relationship of Allergy to Immunity.
Dr. Alexander.
12:00– 1:00 Experimental and Clinical Aspects of Autosensitization.
Dr. Bukantz.

P.M. Session

2:00– 3:00 Student-Faculty Lecture: The Cellular Transfer of Hypersensitiveness.
Dr. Chase.
3:00– 4:00 Serum Sickness and Its Implications.
Dr. Dammin.
4:00– 500 Discussion.

Wednesday, March 5

A.M. Session
9:00–10:00 Systemic Reactions to Drugs.
Dr. Alexander.
10:00–11:00 The Structure and Function of Adrenocortical Steroids.
Dr. Daughaday.
11:00–12:00 ACTH and Cortisone in Allergic Disorders.
Dr. Hampton.
12:00– 1:00 Relation of Allergy to Collagen Diseases.
Dr. Criep.

HEMATOLOGICAL DISORDERS

2:00– 3:00 Immunological Aspects of Transfusion Reactions and the Hemolytic Anemias.
Dr. Moore.
3:00– 4:00 Immunological Aspects of Thrombocytopenic Purpura.
Dr. Harrington.
4:00– 5:00 Discussion.
8:00 Film—Anaphylaxis.

Thursday, March 6

A.M. Session
9:30–10:30 Staff Rounds.
Dr. Wood.

DERMATOLOGICAL ALLERGY

10:30–11:30 Experimental Allergy to Simple Chemical Compounds in Animals.
Dr. Chase.
11:30–12:30 The Eczema Group.
Dr. Rostenberg.

P.M. Session

2:00– 3:00 Drug Eruptions and Ids.
Dr. Rostenberg.
3:00– 4:00 Current Experimental Approaches to Clinical Allergy.
Dr. Bukantz.
4:00– 5:00 Discussion.

Friday, March 7

A.M. Session

THERAPY

9:00–10:00 Prophylaxis in Clinical Allergy.
Dr. Eyermann.
10:00–11:00 Inhalation Therapy of Asthma and Emphysema.
Dr. Eastwood.
11:00–12:00 Allergenic Extracts and Drugs.
Dr. Wilson.
12:00– 1:00 Psychotherapy in Allergic Disorders.
Dr. Gildea.

P.M. Session

2:00– 3:00 Laboratory Demonstrations.
Drs. Bukantz, Noah and Miss Johnson.
3:00– 5:00 General Discussion.

REGIONAL MEETINGS, A.C.P.

NORTH CAROLINA. The 1951 Regional Meeting for North Carolina was held at Duke University, Durham, N. C., December 6, 1951, under the Governorship of Dr. Elbert L. Persons. Dr. Verne S. Caviness, of Raleigh, was the Chairman of the Program Committee, and Dr. James P. Hendrix was Chairman of the Committee on Arrangements. Since 1929, North Carolina has held more or less regular Regional Meetings devoted to College affairs and scientific programs. It was among the first states to organize such meetings. The current program was one of exceptional interest as attested to by the large percentage of member attendance. The meeting was concluded in the evening at the Hope Valley Country Club with Dr. Persons acting as Toastmaster and Dr. Cyrus C. Sturgis, F.A.C.P., Regent of the American College of Physicians and Professor of Internal Medicine and Director of the Simpson Memorial Institute for Medical Research of the University of Michigan Medical School, the speaker of the day.

Coming Regional Meetings

The following regional meetings are scheduled and at the appropriate time the programs will be delivered to all members in the area:

1. EASTERN PENNSYLVANIA, at Philadelphia, January 25, 1952; Dr. Thomas M. McMillan, Governor and General Chairman.

2. COLORADO, at Denver, February 12, 1952; Dr. Ward Darley, Governor, and Dr. A. Ravin, Program Chairman; Dr. Dwight L. Wilbur, San Francisco, A.C.P. Regent, special guest.

3. MIDSOUTH, at New Orleans, La., February 15–16, 1952; Dr. Thomas Findley, Governor and General Chairman; Drs. William C. Chaney, Memphis, David W. Carter, Jr., Dallas, Laurance J. Clark, Jr., Vicksburg, coöperating Governors; Dr. M. C. Pincoffs, Baltimore, A.C.P. President, and Mr. E. R. Loveland, Philadelphia, A.C.P. Executive Secretary, special guests.

4. PUERTO RICO, at San Juan, February 17, 1952; Dr. R. Rodriguez-Molina, Governor and General Chairman; Dr. T. Grier Miller, Philadelphia, A.C.P. President-Elect, special guest.

5. NEBRASKA, at Lincoln, February 23, 1952; Dr. J. D. McCarthy, Omaha, Governor; and Dr. Floyd L. Rogers, Lincoln, General Chairman.

6. VIRGINIA, at Charlottesville, February 28, 1952; Dr. Charles M. Caravati, Richmond, Governor; Dr. James F. Waddill, Norfolk, Secretary; and Dr. Byrd S. Leavell, Charlottesville, Chairman of the Section.

7. MARYLAND, DISTRICT OF COLUMBIA AND DELAWARE, at Baltimore, March 1, 1952; Dr. R. Carmichael Tilghman, Baltimore, Governor and General Chairman; Dr. John Minor, Washington, and Dr. Lemuel C. McGee, Wilmington, cooperating Governors.

8. KANSAS, at Emporia, March 21, 1952; Dr. William C. Menninger, Topeka, Governor, and Dr. Philip W. Morgan, Emporia, Chairman; Dr. M. C. Pincoffs, Baltimore, A.C.P. President, special guest.

9. NEW JERSEY, at Newark, November 5, 1952; Dr. Edward C. Klein, Jr., Governor, and Dr. Henry C. Crossfield, East Orange, General Chairman.

10. MIDWEST, at Chicago, November 22, 1952; Dr. Howard Wakefield, Governor and General Chairman; Dr. Benjamin Wolverton, Cedar Rapids; Dr. James O. Ritchey, Indianapolis; Dr. Douglas Donald, Detroit; Dr. Wesley Spink, Minneapolis; Dr. Charles A. Doan, Columbus; Dr. Karver L. Puestow, Madison; and Dr. J. Murray Kinsman, Louisville; coöperating Governors; Dr. T. Grier Miller, Philadelphia, then A.C.P. President, and Mr. E. R. Loveland, A.C.P. Executive Secretary, special guests.

11. SOUTHEASTERN, at Havana, Cuba, late autumn, 1952; Jose J. Centurion, Governor and General Chairman; Dr. Carter Smith, Atlanta; Dr. William C. Blake, Tampa; and Dr. E. Dice Lineberry, Birmingham, coöperating Governors.

MID-SOUTH REGIONAL MEETING, A.C.P.

LOUISIANA, TENNESSEE, TEXAS, ARKANSAS, MISSISSIPPI, OKLAHOMA

New Orleans, La., February 15 and 16, 1952

Thomas Findley, M.D., F.A.C.P., *General Chairman*

Not since the middle of World War II has New Orleans been the site of a Regional Meeting of the American College of Physicians, but that meeting is still a memorable one—a three-day meeting with a program replete with clinics, panels and scientific general sessions. Physicians with their wives and friends came from all parts of the South, and medical officers of the armed forces attended in large numbers. The program, entertainment, good fellowship, all combined to make it one of the signal regional meetings of the College. That meeting has been a challenge to the General Chairman and to his Committees in preparing the present program and in making the arrangements for the 1952 Mid-South Regional Meeting. The Gov-

ernors of the participating states have added their talents and wholehearted assistance, and members of the College of each state have generously contributed papers.

Members of the College and their ladies, and physicians especially interested in Internal Medicine and this program are cordially invited. Particularly are members encouraged to bring with them young physicians who desire ultimately to qualify as members of the College, in order that they may obtain some insight into the activities and objectives of the College and that Fellows of the College may meet them.

For the Ladies: A special program of entertainment has been arranged for the ladies, and, further, they are especially invited to the Banquet. Tickets will be available on subscription basis at the Registration Desk at the Roosevelt Hotel for the following events:

Friday afternoon—Guided bus tour of the city (approximately $1.00 per person).
Saturday morning—Guided walking tour of the French Quarter (approximately $1.00 per person).
Saturday afternoon—Luncheon at the New Orleans Country Club (approximately $3.00 per person, including transportation by chartered bus).

Banquet: Friday evening, February 15, Gold Room of the Roosevelt Hotel; Reception starts at 6:30. Guests of Honor include Dr. Maurice C. Pincoffs, of Baltimore, Master of the College, its Editor and its President; Mr. Edward R. Loveland, of Philadelphia, Executive Secretary of the College since 1926; and The Honorable Jimmy Arrington, Mayor of Collins, Mississippi.

Tickets must be purchased at the Registration Desk before 1:00 p.m. Friday. Price, cocktails and dinner, $8.00.

Hotel Accommodations: Make your reservations direct with the Roosevelt Hotel, New Orleans, identifying yourself with this Regional Meeting of the American College of Physicians.

SCIENTIFIC PROGRAM

Friday, February 15, 1952

Morning Session

2nd Floor Auditorium, Charity Hospital, 1532 Tulane Avenue

THOMAS FINDLEY, M.D., F.A.C.P., New Orleans

Governor for Louisiana

Presiding

9:00 Welcome.
9:05 Clinical Presentations by Members of the Department of Medicine of the Ochsner Clinic:

(1) Current Concepts in Gout.
Dr. Thomas E. Weiss (by invitation).
(2) The Treatment of Thyrotoxicosis with Radioactive Iodine.
Dr. Paul J. Murison (by invitation).
(3) The Importance of the Early Recognition of Cirrhosis of the Liver.
Dr. William D. Davis, Jr. (Associate).
(4) Tendon Reflexes in Myxedema (Moving Picture).
Dr. A. Seldon Mann, F.A.C.P.
(5) The Treatment of Hemochromatosis by Venesection.
Dr. William R. Arrowsmith (by invitation).

10:35 Intermission.

EDGAR HULL, M.D., F.A.C.P., New Orleans

Presiding

10:45 Clinical Presentations by Members of the Department of Medicine, Louisiana State University School of Medicine.

12:15 Luncheon Recess.

AFTERNOON SESSION

Roosevelt Hotel, University Room

RANDOLPH LYONS, M.D., F.A.C.P., New Orleans

Presiding

2:00 The Glycogen Liver; Two Case Reports in Half Brothers.
DR. R. Q. GOODWIN, F.A.C.P., Oklahoma City, Okla.

2:20 The Pathogenesis and Treatment of Metabolic Alkalosis.
DR. DONALD W. SELDIN (by invitation), Dallas, Tex.

2:40 Some Observations Concerning Vertigo as a Symptom.
DR. OLIVER C. MELSON, F.A.C.P., Little Rock, Ark.

3:00 Primary Malignancy of the Liver.
DR. CONLEY H. SANFORD, F.A.C.P., Memphis, Tenn.

3:20 Intermission.

3:30–5:00
Panel: New Therapeutic Agents, Excluding ACTH and Cortisone. Arranged by DR. EDGAR HULL, F.A.C.P., New Orleans.

EVENING SESSION

(Informal dress)

Gold Room, Roosevelt Hotel

6:30 Cocktails, followed by Dinner.
Toastmaster
DR. THOMAS FINDLEY, Governor for Louisiana.
Guests of Honor
MR. EDWARD R. LOVELAND, Executive Secretary, American College of Physicians.
DR. MAURICE C. PINCOFFS, President, American College of Physicians.
THE HONORABLE JIMMY ARRINGTON, Mayor of Collins, Mississippi.

Saturday, February 16, 1952

MORNING SESSION

2nd Floor Auditorium, Charity Hospital, 1532 Tulane Avenue

CHARLES A. JONES, M.D., F.A.C.P., New Orleans

Presiding

9:00 Clinical Presentations by Members of the Medical Section, Veterans Administration Hospital.

10:30 Intermission.

GEORGE E. BURCH, JR., M.D., F.A.C.P., New Orleans

Presiding

10:40 Clinical Presentations by Members of the Department of Medicine, Tulane University School of Medicine.

12:10 Luncheon Recess.

AFTERNOON SESSION

Roosevelt Hotel, University Room

OSCAR W. BETHEA, M.D., F.A.C.P., New Orleans

Presiding

2:00 Clinico-Pathological Conference.
DR. MAURICE C. PINCOFFS, M.A.C.P., President, American College of Physicians, and Professor of Medicine, University of Maryland School of Medicine, Baltimore, Md.
DR. CHARLES E. DUNLAP (by invitation), Professor of Pathology, Tulane University School of Medicine, New Orleans, La.

3:00 Hyperplasia of the Adrenal Glands.
DR. JAMES A. GREENE, F.A.C.P., Houston, Tex.

3:20 Non-Vascular Cerebral Sclerosis.
DR. PHILIP WORK, F.A.C.P., Gulfport, Miss.

3:40 Intermission.

3:50 Electrolytes in Neuromuscular Disorders.
RICHARD R. OVERMAN, Ph.D. (by invitation), Associate Professor of Physiology, University of Tennessee College of Medicine, Memphis, Tenn.

4:10 Atrial Infarction.
DR. CRAWFORD W. ADAMS (Associate), Nashville, Tenn.

4:30 The Diagnosis and Treatment of Panhypopituitarism.
DR. RAYMOND L. GREGORY, F.A.C.P., Galveston, Tex.

4:50 The Selection of Cases for Valvulotomy.
DR. DON W. CHAPMAN, F.A.C.P., Houston, Tex.

COMMITTEES

Participating Governors

DR. A. A. BLAIR—Arkansas
DR. THOMAS FINDLEY—Louisiana
DR. L. J. CLARK—Mississippi
DR. WANN LANGSTON—Oklahoma
DR. WILLIAM C. CHANEY—Tennessee
DR. DAVID W. CARTER, JR.—Texas

Scientific Program

DR. EDWARD DE S. MATTHEWS, *Chairman*
DR. OSCAR BLITZ
DR. VINCENT J. DERBES
DR. CHARLES A. JONES

Entertainment

DR. A. SELDON MANN

Ladies' Committee

Mrs. Thomas Findley, *Chairman*
Mrs. Edward de S. Matthews
Mrs. Gordon McHardy
Mrs. Norton W. Voorhies

The American Academy of Allergy Offers Postgraduate Courses

The American Academy of Allergy is offering two postgraduate courses at Chicago, Ill., February 15, 16 and 17, 1952—"Technics of Experimental Immunology as Applied to Allergy," at the Hotel Sherman, and "Identification and Biology of Fungi and Pollen," at Northwestern University Medical School. The registration fee for the entire course or any part of it is $25.00. Physicians may attend either course completely or divide their time as they choose between the two courses. For course outlines and additional data, consult the Academy's Executive Offices, 208 E. Wisconsin Ave., Milwaukee 2, Wis. The Annual Meeting of the Academy will be held at the Hotel Sherman, Chicago, February 18, 19 and 20.

The 48th Annual Congress on Medical Education and Licensure will be held February 10–12, 1952, in the Palmer House, Chicago, Ill. The Congress is conducted under the auspices of the Council on Medical Education and Hospitals of the A.M.A. and the Federation of State Medical Boards of the United States.

Oral Examinations, American Board of Internal Medicine

Oral examinations will be given during 1952 by the American Board of Internal Medicine at New Orleans, February 14, 15 and 16; at Cleveland, April 17, 18 and 19; and at Chicago, on Thursday, Friday and Saturday, preceding the meeting of the American Medical Association during June.

The American Board of Pediatrics—Oral Examinations

The American Board of Pediatrics has announced oral examinations to be held in New York, N. Y., February 1–3, 1952, and in St. Louis, Mo., March 21–23, 1952.

Mississippi Valley Medical Society 1952 Essay Contest

The Twelfth Annual Essay Contest of the Mississippi Valley Medical Society will be held in 1952. The Society will offer a cash prize of $200.00, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics and education) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. The winner will be invited to present his contribution before the 17th Annual Meeting of the Mississippi Medical Society to be held in St. Louis, Mo., October 1–3, 1952. All contributions must be received not later than May 1, 1952. Further details may be secured from: Harold Swanberg, M.D., F.A.C.P., Secretary, Mississippi Valley Medical Society, 209–224 W.C.U. Bldg., Quincy, Ill.

The International Diabetes Federation has announced it is sponsoring a congress on diabetes mellitus, to be held at Leyden, Netherlands, July 7–12, 1952. Further details may be obtained by applying to Dr. F. Gerritzen, 33 Prinsegracht, The Hague, Netherlands.

Armed Forces Surgeons General Acclaimed by A.P.M.A.

In recognition of the fine achievements of the medical services of the armed forces, the American Pharmaceutical Manufacturers Association has presented its 1951 Scientific Award to the Surgeons General of the U. S. Army, Navy and Air Force. Recipients of the award were Major General George E. Armstrong, (MC), U.S.A., F.A.C.P.; Rear Admiral H. Lamont Pugh, (MC), U.S.N., F.A.C.P., and Major General Harry G. Armstrong, (MC), U.S.A.F., F.A.C.P.

The Division of Graduate and Postgraduate Medical Education of the University of Utah College of Medicine presented a postgraduate course, "The Functional Aspects of Medical Practice," at the Salt Lake General Hospital, November 29-December 1, 1951. Fellows of the American College of Physicians who participated on the program were Dr. Theodore C. Bauerlein, Assistant Clinical Professor of Medicine; Dr. Charles H. Hardin Branch, Professor and Head of the Department of Psychiatry, and Dr. Louis G. Moench, Assistant Clinical Professor of Medicine.

The following Fellows of the College attended the Third Annual Meeting of the Medical Council of the Silver Hill Foundation, New Canaan, Conn., on October 13 as guests of Dr. William B. Terhune, F.A.C.P., Medical Director: Dr. Harold L. Amoss, Greenwich, Conn.; Dr. Dana W. Atchley, Dr. Ralph H. Boots, Dr. Russell L. Cecil, Dr. Frank H. Peters and Dr. Cornelius H. Traeger, all of New York, N. Y.; Dr. Kendall A. Elsom and Dr. T. Grier Miller of Philadelphia, Pa.; Dr. Dwight L. Siscoe, Boston, Mass.; Dr. Warren I. Titus, Glen Cove, N. Y.; Dr. Elihu S. Wing, Providence, R. I.

The Silver Hill Foundation is a psychotherapeutic unit devoted to the study, care and treatment of the psychoneuroses where patients are given brief, intensive psychotherapeutic and physiological aid in rehabilitating and re-establishing their lives. The Medical Staff is composed of internists who, although they are Diplomates of the American Board of Psychiatry and Neurology, employ the eclectic approach in the treatment of the psychoneuroses rather than adhering to any one formal school of psychiatry. The subject for discussion of the Council this year was "Occupational and Avocational Therapy," coinciding with the dedication of a new, modern, Avocational Therapy Building.

Dr. Hobart Reimann, F.A.C.P., formerly Professor of Medicine at Jefferson Medical College of Philadelphia, was given an award for "Distinguished Service in Medical Education" by his alma mater, the University of Buffalo School of Medicine, on December 8, 1951.

Dr. Raymond B. Allen, F.A.C.P., President of the University of Washington, has resigned to accept an appointment by President Truman as Director of the Psychological Strategy Board early in January. Dr. Allen was formerly Dean of the University of Illinois College of Medicine and Executive Dean of the Chicago Colleges of that University. He went to Seattle in 1946, as President of the University of Washington. The Board has been headed by Gordon Gray, President of the University of North Carolina, who is planning to return to his University post.

Dr. Allen, since going to the University of Washington, was a member of the Eberstadt Committee of the Hoover Commission, was director of medical services for the National Military Establishment, and more recently acted as chairman of the Salary Stabilization Board of the Economic Stabilization Agency.

Northwestern University held its Centennial Convocation in Cahn Auditorium, Evanston, December 2, 1951, the chief purpose being to honor one hundred men and women selected for distinguished service to society while residing in Illinois, Indiana, Michigan, Minnesota, Ohio or Wisconsin. These states comprised the Northwest Territory from which Northwestern University took its name one hundred years ago.

Among those to receive the Centennial Awards were the following members of the American College of Physicians: Dr. Herman N. Bundesen, F.A.C.P., Chicago, Ill.; Dr. A. J. Carlson, M.A.C.P., Chicago, Ill.; Dr. Phillip S. Hench, F.A.C.P., Rochester, Minn.; Dr. James B. Herrick, M.A.C.P., Chicago, Ill.; Dr. Howard T. Karsner, F.A.C.P., Washington, D. C.; Dr. William S. Middleton, F.A.C.P., Madison, Wis.

At the Annual Meeting of the Board of Directors of the Mississippi Valley Medical Society held in Quincy, Ill., November 18, 1951, Dr. Daniel L. Sexton, F.A.C.P., St. Louis, Mo., assumed the office of President; Dr. John I. Marker, F.A.C.P., Davenport, Iowa, was elected President-Elect; Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., was re-elected Secretary-Treasurer; and Dr. Alphonse McMahon, F.A.C.P., St. Louis, Mo., was elected Chairman of the Board of Trustees. The next Annual Meeting of the Association will be held in St. Louis, Mo., October 1–3, 1952, and the Annual Meeting of the American Medical Writers' Association will be held in conjunction with the Society's meeting on October 1.

Dr. William M. Sheppe, F.A.C.P., Department of Internal Medicine, The Wheeling Clinic, Wheeling, W. Va., has been elected President of the West Virginia Diabetes Association to succeed Dr. George P. Heffner, F.A.C.P., Charleston, W. Va.

Under the secretaryship of Dr. William M. LeFevre, F.A.C.P., the Western Michigan Group of the American College of Physicians held a Regional Meeting at Lansing, November 14. The program consisted of a tour of the Michigan Department of Health Laboratories, under the supervision of Dr. G. D. Cummings, Director of Laboratories, of a reception and dinner at the Hotel Olds and of a formal presentation by Dr. Christopher J. Stringer, F.A.C.P., Medical Director of the Ingham County Sanatorium, on "Pulmonary Diseases." The group proposes to hold a spring meeting at Battle Creek and an autumn, 1952, meeting at Muskegon.

Dr. Joseph W. Post, F.A.C.P., became President of the Philadelphia County Medical Society, January 1, 1952, succeeding Dr. Louis B. Laplace, F.A.C.P., retiring President. Dr. Truman G. Schnabel, F.A.C.P., has been chosen President-Elect. Dr. Malcolm W. Miller, F.A.C.P., has been re-elected Secretary.

Dr. Thomas J. White, F.A.C.P., Jersey City, was recently elected President of the New Jersey Heart Association.

The Right Hon. Lord Moran, M.C., M.D., F.R.C.P., F.A.C.P. (Hon.), has accepted the office of President of the Health Congress of the Royal Sanitary Institute, which is to take place at Margate, England, April 22–25, 1952.

Francis G. Blake, M.D., F.A.C.P., Sterling Professor of Medicine at Yale University School of Medicine, New Haven, has been granted leave of absence starting

January 1, 1952, to become Technical Director of Research, Medical Research and Development Board, Office of the Surgeon General, Department of the Army. Dr. Blake will officially retire as Sterling Professor of Medicine at Yale on June 30, 1952.

Dr. Stefan S. Fajans has concluded a Research Fellowship under the auspices of the American College of Physicians, and has now been appointed Assistant Professor of Internal Medicine at the University of Michigan Medical School, beginning July 1, 1952.

Dr. Eli H. Rubin, F.A.C.P., New York, N. Y., was guest speaker at a meeting of the Medico-Chirurgical Society of Montreal, Canada, on November 2, 1951. His subject was "The Lung as a Mirror of Systemic Disease." On November 3, 1951, he participated in a chest conference at the Jewish Hospital, Montreal.

The Division of Biological Sciences of the University of Chicago has announced the promotion of Dr. Leon O. Jacobson, F.A.C.P., and Dr. Joseph B. Kirsner, F.A.C.P., to the rank of Professor of Medicine.

Dr. Margil C. Carlisle, F.A.C.P., Waco, was elected Secretary of the Texas Pediatric Society at its meeting last October.

OBITUARIES

DR. JOHN HAROLD MILLS

John H. Mills, A.B., M.D., M.S., F.A.C.P., who served in the capacity of Chief of the Medical Service, Veterans Administration Hospital, Portland, Ore., for the last five years, died on October 14, 1951.

Dr. Mills was born in Liverpool, England, of American parents, on May 19, 1902. He received his A.B. degree in 1924 from the University of Illinois and his M.D. degree from the University of Chicago in 1932. In 1937 he received the degree of M.S. (Med.) from the University of Minnesota.

Dr. Mills was Associate in Medicine at the University of Maryland School of Medicine, 1937–1938, following which he started practice in Chicago, moving in 1941 to Spokane, Wash. He entered active service as Major, Medical Corps, Army of the United States, in October, 1942, serving until June, 1946, when he was discharged with the rank of Colonel. His last assignment in the Army was as Chief of the Medical Service, 313th General Hospital. Following his active duty, Dr. Mills accepted staff appointment in the Veterans Administration with assignment to the Veterans Administration Hospital, Portland, Ore., where he served in the capacity of Chief of the Medical Service up to the date of his death.

Dr. Mills was certified by the American Board of Internal Medicine in 1939 and became a Fellow of the American College of Physicians in the same year. He was a member of Delta Tau Delta and Phi Rho Sigma Fraternities, and held membership in two honor societies, Sigma Xi and Alpha Omega Alpha. He made many contributions to various scientific and medical societies.

Dr. Mills was a highly qualified internist, an exceptionally able teacher, and had an outstanding record of accomplishment at the Veterans Administration Hospital in Portland. He was extremely well liked by the veteran patients and was very popular among his friends and associates, who will keenly feel his passing.

J. T. Boone (MC),
Vice Admiral, U. S. Navy, Retired,
Governor for the Veterans Administration

DR. WILLIAM BRADFORD NEWCOMB

William Bradford Newcomb, M.D., F.A.C.P., was born in Gloucester County, Va., July 28, 1886, and died on August 1, 1951, at the age of 65 of congestive heart failure. He was unmarried and is survived by a sister, Mrs. Hunter Gates, and one brother, Dr. John Lloyd Newcomb, the retired President of the University of Virginia.

After having received an A.B. in 1906 from William and Mary College, he graduated in Medicine from Johns Hopkins University in 1910. He interned in New York Hospital, 1910–12, and was Assistant Pathologist there, 1912–13. He began the practice of Internal Medicine in Norfolk in 1913 and was an active clinician and a respected consultant in that city until his final illness. Though Internal Medicine was his specialty, he continued an active interest in Pathology and aided local hospitals in the development of the laboratories.

In World War I Dr. Newcomb served on the Selective Advisory Board and in World War II he organized a special reserve unit of the United States Public Health Service.

Dr. Newcomb was on the attending staff of De Paul, Norfolk General, and Leigh Memorial Hospitals; he was a Diplomate of the American Board of Internal Medicine and a former President of the Norfolk County Medical Society. He was a

member of the Virginia Medical Society, and the Southern Medical Association and had been an active Fellow of The American College of Physicians since 1934.

He was a lover of sports and an ardent horseman. His many friends and his colleagues, to whom he was an outstanding counsellor, will miss his warmth and his inspiring friendship.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

DR. ADA ESTELLE SCHWEITZER

Ada Estelle Schweitzer, M.D., F.A.C.P., was born August 29, 1872, at LaGrange, Ind., and died on July 2, 1951, at the age of 78 years of cerebral hemorrhage. She received her early education in the schools of Indiana and Michigan. She graduated in 1906 from the Indiana Medical College (later Purdue University).

She served for a time as Associate Professor in Bacteriology at Indiana Medical College. From 1913 to 1917 she was bacteriologist with the Indiana State Board of Health. She was head of the child hygiene division of the Indiana State Board of Health from 1919 to 1933. During her tenure with the Indiana State Board of Health she was granted leaves of absence for special services in the Federal Government. In 1927 she represented the United States as an official delegate at the Pan-American Health Congress at Havana, Cuba. During the memorable influenza epidemic her work in South Carolina brought a government commendation. As a result of her ability and early interest in Public Health and Public Health Education, she was named, in 1934, to direct the Federal Emergency Education Program in Indianapolis. She served several years as Health Chairman, Indiana Council of Womens' Clubs. At one time Dr. Schweitzer was Vice President of Indianapolis Medical Society. Among her many activities and memberships might be mentioned the American Public Association, the American School Hygiene Association, the American Academy of Pediatrics and the American Social Hygiene Association, as well as the Indianapolis, Indiana State and American Medical Associations.

Dr. Schweitzer was one of the first three women inducted to Fellowship in the American College of Physicians back in 1920, the three being inducted at the same time. Dr. Schweitzer maintained a close and abiding interest in the College through the many years she was a Fellow. She retired because of illness in 1945 and became a helpless invalid in 1948.

During her days at the Indiana State Board of Health she wrote many books and pamphlets on care of the baby, care of the mother and many others.

She was one of those individuals who devoted her all to the making of good health a reality.

JAMES O. RITCHEY, M.D., F.A.C.P.,
Governor for Indiana

DR. JOHN A. WENTWORTH

John Alexander Wentworth, M.D., F.A.C.P., was born in Portland, Maine, on April 26, 1888. He graduated from Bowdoin College in 1909 with the degree of Bachelor of Arts and from Harvard Medical School in 1913. His postgraduate work was done at Peter Bent Brigham Hospital, at Harvard Medical School, and in London and Paris. During the first World War, he served in the Medical Corps, U. S. Army, as Associate Director of the pathological laboratory at Camp Devens, Mass., and as Director of the pathological laboratory, Base Hospital 107.

A diplomate of the American Board of Internal Medicine, he had been a member of the College since 1931. Other memberships included American Medical Associa-

tion, Connecticut State Medical Association, American Heart Association and the American College of Chest Physicians.

In ill health for several years, he had been in retirement since 1945, and died on September 17, 1951, of cerebral hemorrhage.

Dr. Wentworth was respected by his confreres as an able clinician and beloved by all who knew him.

THOMAS P. MURDOCK, M.D., F.A.C.P.,
Governor for Connecticut

DR. HARRISON ALONZO WIGTON

Harrison Alonzo Wigton, M.D., F.A.C.P., passed away on October 9, 1951, in Omaha, where he had practiced medicine since 1909.

Dr. Wigton was born in Hastings, Nebraska, December 20, 1878. He was graduated from the Omaha High School in 1897, received his Bachelor of Science degree from Hastings College in 1900 and his Doctor of Medicine degree from the University of Nebraska College of Medicine in 1905. He served as Assistant Superintendent of the Lincoln State Hospital in Lincoln, Nebraska, from 1906 to 1909, following which he opened an office in Omaha, where he practiced until his death.

He was appointed to the teaching staff of the University of Nebraska College of Medicine in 1914 as Assistant in Pediatrics, became Instructor in Neuropsychiatry in 1918, Assistant Professor in 1922, Associate Professor in 1932 and was advanced to Professor Emeritus in 1947.

He was neuropsychiatrist at the Douglas County, Immanuel, Lutheran, Nebraska Methodist, Clarkson and University of Nebraska Hospitals.

Dr. Wigton was a Fellow of the American College of Physicians (1929), Diplomate of the American Board of Psychiatry and Neurology (1940), Fellow of the American Medical Association, member of the Nebraska State Medical Association, Omaha-Douglas County Medical Society, Charter Member of the Omaha Mid-West Clinical Society and past secretary of the Missouri Valley Neuropsychiatric Society. He was a Trustee of Hastings College.

Dr. Wigton was also a member of the Nebraska State Historical Society, Nebraskana Society, Kiwanis, Scottish Rite and Shrine.

Survivors include his widow, Mrs. Jessie May Wigton, three children and seven grandchildren. Robert S. Wigton, M.D., like his father, is a neuropsychiatrist.

The College and the medical profession as a whole have suffered a real loss in the passing of Dr. Wigton.

J. D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

ABRIDGED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 18, 1951

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, Pa., Sunday, November 18, 1951, beginning at 9:50 a. m. President Maurice C. Pincoffs presided, and Mr. E. R. Loveland acted as Secretary, with the following in attendance: Maurice C. Pincoffs, *President;* T. Grier Miller, *President-Elect;* LeRoy H. Sloan, *First Vice President;* Walter B. Martin, *Second Vice President;* Howard P. Lewis, *Third Vice President;* William D. Stroud, *Treasurer;* Richard A. Kern, *Secretary-General;* Edward L. Bortz, Harold H. Jones, Charles F. Moffatt, Dwight L. Wilbur, A. B. Brower, Alex. M. Burgess, Reginald Fitz, George H. Lathrope, Cyrus C. Sturgis, Asa L. Lincoln, J. Owsley Manier, Walter L. Palmer, Wallace M. Yater, Thomas M. McMillan, *Chairman, Advisory Committee on Postgraduate Courses;* Thomas Findley, *Guest.*

The only absentees were Dr. Marion A. Blankenhorn, Dr. William S. McCann, and Dr. Charles A. Doan, Chairman of the Board of Governors.

In view of the fact that the Minutes of the preceding meetings of the Board of Regents had been published in the ANNALS OF INTERNAL MEDICINE, it was moved by Dr. LeRoy H. Sloan and seconded by Dr. Walter B. Martin, and unanimously carried, that the Minutes be approved as published and not read at this meeting.

The Secretary presented the following communications:

(1) Letters or reports on the absent Regents, Dr. Marion A. Blankenhorn, Dr. William S. McCann and Dr. Charles A. Doan, the latter having been present for Committee meetings the day before, but having other duties preventing his attendance at the Regents' meeting;

(2) Announcement that President Pincoffs had appointed Dr. John R. Paul, F.A.C.P., New Haven, Conn., Dr. Dorothy M. Horstmann (Associate), New Haven, Conn., and Dr. Joseph F. Paquet (Associate), Portland, Ore., as representatives of this College at the Second International Poliomyelitis Conference, Copenhagen, Denmark, during September, 1951;

(3) Announcement of the appointment by President Pincoffs of Dr. Howard Wakefield, Governor for Northern Illinois, as representative of the College at the inauguration of Lawrence A. Kimpton as Chancellor of the University of Chicago, October 8, 1951; also as representative of the College at the Medical Civil Defense Conference at Chicago, November 9–10, 1951;

(4) Announcement of the appointment by President Pincoffs of Dr. Leslie R. Kober, Governor for Arizona, as official representative of the College at the inauguration of Richard Anderson Harvill as President of the University of Arizona;

(5) Announcement of the attendance of President-Elect T. Grier Miller as official representative of the College at the Convocation and meeting of the Royal College of Physicians of Canada at Quebec, September 28–29, 1951;

(6) Announcement of the attendance of President Maurice C. Pincoffs, Dr. John Minor, Governor for the District of Columbia, and Dr. Eugene C. Eppinger, F.A.C.P., Boston, Mass., as representatives of the College at the Civil Defense Conference of the Federal Civil Defense Administration at Washington, D. C., May 7–8, 1951;

(7) The reading of a letter of appreciation from Sir John Parkinson for all courtesies extended during his visit to America in connection with our last Annual Session at St. Louis;

(8) A letter of appreciation to the Officers and Regents of the College from Dr. Wilfred Evans, a Fellow of the Royal Australasian College of Physicians, for our having arranged a fairly extensive itinerary for inspection of medical institutions in this country;

(9) Acknowledgment of the recognition by the American Medical Association of the work of the Conference Committee on Graduate Training in Medicine, in connection with the published list of approved hospitals for residencies and fellowships;

(10) A communication from Dr. Carter Smith, Governor for Georgia, relating to the wishes of the late Dr. James E. Paullin, M.A.C.P., who died suddenly August 13, 1951, in which it was requested that instead of the College or its Regents and Governors sending a floral tribute for his funeral that such funds be used instead as donations to the "James E. Paullin Scholarship Fund of Emory University School of Medicine."

The Secretary reported that Dr. Charles F. Martin, M.A.C.P., of Montreal, and Miss Pearl M. Ott, Executive Assistant, had transmitted $50.00 and $25.00, respectively, through the College Office.

After some discussion it was moved by Dr. C. C. Sturgis, seconded by Dr. A. B. Brower, and unanimously carried, that the President and the Executive Committee determine upon the amount of money to be contributed by the College to the Paullin Scholarship Fund, and, furthermore, that any individual Regent, Officer, Governor or Member of the College, who might be inclined to send a personal contribution to this Fund may do so through the College Office and all such contributions shall be transmitted by the Secretary, detailing the personal contributions as well as the College donation.

(11) A communication concerning the status of the present Committee on Military Affairs of the College, which was appointed a year ago more or less as a temporary Committee.

On motion by Dr. Walter B. Martin, seconded and regularly carried, it was

RESOLVED, that the Committee on Military Affairs be a continuing Committee, appointments thereto to be made by the President.

PRESIDENT MAURICE C. PINCOFFS: "We shall now proceed with the regular Agenda of this meeting. First will be the report of the Secretary-General, Dr. Richard A. Kern."

Dr. Richard A. Kern, Secretary-General, reported the deaths of 2 Masters, 31 Fellows and 8 Associates since the last meeting of the Board of Regents, and their names were recorded in the Minutes. Among those deceased were Dr. James E. Paullin, of Atlanta, Ga., former Regent and President of the College, Dr. Harvey G. Beck, of Baltimore, Md., former Governor of the College, and Dr. Ada Estelle Schweitzer, of Indianapolis, Ind., one of the first three women elected to Fellowship in the College (1920).

Dr. Kern then recorded the names of 21 new Life members, which brought the grand total to 949, of whom 97 are deceased, leaving a balance of 852. The names of the new Life Members were spread upon the Minutes, and the report of the Secretary-General was duly accepted.

PRESIDENT PINCOFFS: "Next will be the report of the Executive Secretary, Mr. E. R. Loveland."

MR. E. R. LOVELAND: "Much of the information that might be included in this report will be revealed through individual Committee reports. However, I would like to bring out a few of the highlights of the past year's operations:

New Elections:

		Fellows	*Associates*
Annual Session Report:	1949–50	300 (31 direct)	473
	1950–51	327 (13 direct)	400

"It is interesting to note that the average number of elections to Associateship for the past four years has been 425. It is also interesting to observe that for the two years preceding the 1949–50 Annual Session, the number of elections to Fellowship was 244; also that the number of elections to Direct Fellowship have been markedly reduced regularly, 46 in 1947, 43 in 1948, 31 in 1949 and 13 in 1950.

"Resignations and Dropped Members: There has only been an average of one Fellow per year who has resigned, and 1.5 Fellows per year who have been dropped for delinquency or other reasons. Currently, the only resignation among the Fellows is the former Governor for the Navy, who is an Ophthalmologist and who merely accepted Fellowship as a matter of routine, because as Surgeon General he had to be the College Governor for the Navy. For the year ending with our St. Louis Session there were 168 Associates who resigned or were dropped because they could not qualify for Fellowship. The average, however, for the preceding three years was 59, less than 14% of the number of new elections to Associateship. Many on the Board of Governors and on the Board of Regents were misled from the numbers of resigned and dropped Associates at the St. Louis Session. It was a thoroughly unrepresentative year, because it represented the culmination of the terms of Associates who had been elected as far back as 1940, but whose Associate terms were extended by the Regents due to military service. Those who resigned or were dropped represented an accumulation of the less qualified Associates elected over a period of ten or eleven years, and it is not to be expected that the same experience will occur in the foreseeable future. Therefore, the great alarm that some felt was not justifiable, for it represented no definite trend.

"During the last several months we have conducted extensive membership studies and obtained the analysis by an expert actuary, whose services were employed on the recommendation of the Governors' Survey Committee and President Pincoffs. There was no budget appropriation for the study, and we do not yet have the actuary's bill and cannot predict exactly what it will be, although we do not estimate that it will amount to more than three or four hundred dollars. The findings will probably be revealed in the report of the Governors' Survey Committee.

"Regional Meetings: During the calendar year 1951, 23 have been scheduled with an estimated gross attendance of 2,700. Several additional Regional Meetings are already scheduled for the winter months. A list of the meetings has been duplicated for your information. Our observations are that the one or two-state Regional Meetings are more effective than the large multi-state meetings. For example, the Oklahoma-Arkansas Regional Meeting, held at Hot Springs, had an 80% membership attendance from Arkansas and a 38% membership attendance from Oklahoma. In comparison, let us take the Midwest Regional Meeting, held at Columbus, where eight states were represented. This appeared like a large meeting, and those in attendance were enthusiastic about it; the program was excellent, but the percentage of attendance by members was definitely poor; to wit: Ohio, 10%; Illinois, 4.3%; Michigan, 5.4%; Indiana, 17%; Minnesota, 1%; Wisconsin, 1.7%; Iowa, 1.5%; Kentucky, 6%. The multi-state meetings provide less intimate contact among the members, afford fewer opportunities for the younger members to get a place on the program and do not provide adequate opportunity for the members of any one state to meet

prospective candidates for membership from their respective territories. The Midwest Regional Meeting is not singled out as a special example; the same experience occurred with the New England Regional Meeting, where six states and two provinces were combined, and the Southeastern Regional Meeting, the latter to a less degree.

"Postgraduate Courses: During the year 1951 we will have conducted a total of 17 courses, with a registration of 505 for the first 8 during the spring, and more than 600 (registrations not yet complete) for the last 9 courses in the autumn. These continue to be the most popular activities of the College among the members, and it would appear from the reports that are obtained on request from each registrant that the quality of the courses is constantly improving. The registrants are in no sense limited to the younger members of the College, the courses being patronized by members of all ages; oftentimes members beyond sixty years of age.

"Annals of Internal Medicine: During the past year the circulation of the Annals has increased to slightly over 15,000 copies per month, not as large an increase as in the preceding three years, but still progressing. Although the number of pages has been increased by 36% and the cost of printing and postage commensurately increased, yet the surplus has been maintained within $1,800.00 of that for the previous year.

"Directory: The assembling of the biographical data of all the members for publication in the Directory is becoming more and more a laborious and time-consuming job; all copy has long since been released to the printer and the first portion of the book is on the presses, but it is not anticipated that the Directory will be ready for delivery until toward the end of the current year.

"32nd Annual Session, St. Louis—attracted a gross registration of only 3,259, the smallest registration since the Annual Session of 1942 in St. Paul. Of this number, there were only 2,284 physicians, of whom only 1,564 were members of the College, which is about 22% of the members, compared with former averages of about 33% of the members. The opinion of the program among members was somewhat diversified, and many decried the absence of any entertainment features for the members or for the wives. Our exhibitors subscribed to more space than customary with the expectation of the usual size of the College meeting, with the result that some exhibitors were not fully satisfied with the attendance at their booths. This may be reflected in a smaller exhibit in 1952. It is interesting to note that the exhibits and guest fees of non-members more than paid for the entire St. Louis Annual Session, leaving a net surplus of some $5,600.00.

"Two new features at the St. Louis Session were the preparation of a highlight moving picture of the Session, paid for by Wyeth, Incorporated, and a trial at recording the Panel Discussions on recording tape, paid for by Smith, Kline & French. The recordings of the Panels were not satisfactory, or of any practical use, because of mechanical difficulties and the absence of identification of changing speakers.

"The Tele-Clinic, or motion picture, is generally considered very successful. The film has been shown at many Regional Meetings and other groups of physicians, such as Journal Clubs, etc. It is estimated by Dr. George E. Farrar, Jr., of Wyeth, Incorporated, that the film will be viewed by some 15,000 doctors during the year. A copy of the film has been deposited with the College for current use and future historical value. Wyeth is interested in and perfectly willing to make another such motion picture of the Cleveland Session.

"College Staff: In the Philadelphia area, as in many others, there is a marked shortage of competent office personnel, especially stenographers, secretaries and bookkeepers. The College must not only compete with industry, but with Government. The Federal Government is constantly giving examinations and broadcasting by radio for new employees with not too marked qualifications, but at salaries ranging from $2,475.00 per annum up to $3,200.00 per annum, the maximum available in a very brief period of time. This past summer we experienced more difficulty than ever

before in keeping our staff intact. In fact we didn't keep it intact and had a number of resignations. However, I believe we were benefited thereby, because it is my feeling that we now have one of the finest staffs we have had in many years. The salaries offered by the College are not as high as the Government is offering, nor as high as many receive in industry, but the tenure and conditions of work are superior, and we believe the type of work more inspiring. Our salaries are probably comparable or better than some educational institutions, but we require a higher quality of work and, perhaps, more hours than universities and similar institutions demand. If we want to keep a superior staff we must be prepared to pay salaries commensurate with those of our competitors. In the long run, a well paid and satisfied competent employee is worth much more than two poorly paid, discontented and incompetent persons. I hope the Board of Regents and the Finance Committee, as they have in the past, will extend to us such leeway in adjusting salaries of competent employes as necessity and good judgment may dictate.

"Lastly, we are gratified with the financial experience of the year. The income has been some $74,000.00 greater than anticipated, and the expenditures $4,000.00 less than the budget, with the prospect of a surplus for the combined Endowment and General Funds of $97,000.00.

"With an income of some $335,000.00 per annum, largely in small items of $15.00, $20.00 and $30.00, this entails an enormous amount of routine bookkeeping. Our bookkeeping system, installed twenty-five years ago, still adequately records the financial transactions of the College, but being a wholly hand system entails more time and more expense than a modern machine bookkeeping system would require. However, the installation of a modern system would cost a considerable amount, probably $3,700.00. We believe it would be more than justified, however, for the benefit of the future. It would require a year or so to completely install the system and train our bookkeeper therein, and it seems to us wise to set this necessary department in shape while funds are more than adequately available and to have it working well while your incumbent Executive Secretary is in office—not that he is considering termination of services, but merely thinking that time is short and in less than seven years more he will have reached the age of retirement."

PRESIDENT PINCOFFS: "Thank you, Mr. Loveland. I am sure we all express the feeling of the Regents of the appreciation for the enormous amount of work that is so well done in your office.

"I wish to report to the Regents the action of the Executive Committee on two matters. At the meeting in St. Louis the Executive Committee was given authority to approve the recommendation of the Committee on Fellowships and Awards in regard to the recipients of the John Phillips Memorial and the James D. Bruce Memorial Awards. Formerly such approval was not obtained until the autumn meeting of the Regents, and the Committee felt that they were very handicapped in obtaining suitable recipients at such a late date. The receipt of these Awards is more or less contingent on the appearance of the recipients at the meeting. This year the Committee has nominated Dr. Andre F. Cournand, of New York, N. Y., for the John Phillips Memorial Award, and Dr. James H. Gear, of the South African Institute for Medical Research, Johannesburg, South Africa, for the James D. Bruce Memorial Award, and these nominations have been approved and confirmed by the Executive Committee. These Awards seem well in line with the high standards for such Awards in the past, and both recipients have accepted.

"The Executive Committee of the College has also had to deal with the problem of the Joint Commission on the Accreditation of Hospitals. We have been represented at the preliminary meetings by Dr. LeRoy H. Sloan and Dr. Edward L. Bortz, and Dr. William S. Middleton, during his Presidency, took an active interest in the matter. Last spring the Regents authorized the President to appoint the three Com-

missioners of our College on the governing body, and, also, with the concurrence of the Executive Committee, to appoint our representative on the Advisory Committee. The Advisory Committee, together with the Director, will be the actual executive body of the Joint Commission. The incorporation of the Joint Commission has reached the point where it only needs the signatures of the Commissioners. The three Commissioners from our College, whom I have appointed, are as follows:

Dr. LeRoy H. Sloan, Chicago, Ill. ..... three years
Dr. William S. Middleton, Madison, Wis. ..... two years
Dr. Alex. M. Burgess, Providence, R. I. ..... one year

"Yesterday at the meeting of the Executive Committee of the College, Dr. LeRoy H. Sloan acquiesced to assume the additional burden of being a member of the Advisory Committee. In his opinion and in my mind, and in that of all those who have studied this question, this is going to be the key body, the executive body of the Joint Commission, and it was felt by the Executive Committee and by me that no one else is as well qualified through his long experience and interest in this question as Dr. Sloan. His willingness to assume this burden deserves the thanks of all of us.

"This report requires no action by the Regents, since the authority was previously granted to the Executive Committee to carry out these actions.

"The appointment of Dr. Sloan to the Advisory Committee probably will require the appointment of another member of the Commission to make our three complete. That authority was granted by the Regents to the President, and unless the Regents at this time feel that it should be undertaken in some other way, I shall assume that I still have that authority.

"May we now have the report of the Committee on Educational Policy by Dr. Edward L. Bortz, Acting Chairman?"

Dr. Edward L. Bortz: "The Chairman of our Committee, Dr. Marion A. Blankenhorn, was unable to be here, but he has written a letter for the consideration of the Committee from which we herewith quote as our report:

'On reviewing some of our older records, I find that a rather broad commission was given to this Committee, charging it with correlation of all the educational efforts of the College, Postgraduate Courses, Research Fellowships, programs of Annual Sessions and Regional Meetings, etc. I learn also that one of the proposals was that the Annual Session programs, rather than being the product essentially of the President and of the General Chairman, should be one supervised by this Committee. Nothing was ever done to implement this proposal, although the Board of Regents approved it. It is my belief now that this was too large an undertaking even with any kind of implement. For that reason the Committee did in 1950 report to the Regents as follows—we believe that the College by its present methods, that is, through its journal and its Annual Sessions, is accomplishing its educational functions, and the Committee offers advice only when requested. It should be noted then that Dr. William S. Middleton, then President, did not ask any advice of this Committee, although Dr. Middleton did ask abundant advice from the Chairman and others individually. The present President, Dr. Maurice C. Pincoffs, likewise has not made a direct request to this Committee, probably because he knows that the Committee is not very well qualified to give the advice he desires. Nonetheless, I think the Educational Policy Committee should develop methods to become qualified. Perhaps now, by making a critical review of the educational efforts and the success of the Annual Session programs, this could be accomplished. My own experience with the educational efforts of Regional Meetings of the College, of meetings of the American Medical Association, of state meetings, of the meeting of the Central Society for Clinical Research, and others, leads me to believe that a satisfied customer is the best

criterion of the success of any meeting. Mr. Loveland's collected criticisms of the various Postgraduate Courses given by the College develops valuable information as to the success of individual courses. The Committee on Educational Policy should devise some method of collecting expressions of satisfaction or of dissatisfaction which may lead to devising the best programs possible for the Annual Sessions or for Regional Meetings. At the recent St. Louis Session, where many panels and group discussions were readily available and near at hand, attendance on such panels was, in my observation, a good guide to their value. I think a record should be kept of such attendance. Other methods of sampling audience response can be devised. Observations could be made to learn the value of various television and motion picture performances. In my opinion, some were good and some were poor. My frequent sampling of many of these visual aids to teaching convinces me that the good show gets the crowds, and by good show I do not mean only a novel and exciting one. I suggest the Committee on Educational Policy be considerably enlarged for the purpose of collecting information at the coming Annual Session which will be useful in establishing an educational policy.'

"My own particular reaction to the participation of the Committee on Educational Policy in the Annual Session programs is that we already have a President's Consulting Committee on Annual Sessions, made up of the President and General Chairman of the last three Annual Sessions. It would be duplication to have the Educational Committee working on the same thing.

"The Committee on Educational Policy has in the past worked closely with the Advisory Committee on Postgraduate Courses, the latter being a Committee of the Board of Governors."

PRESIDENT PINCOFFS: "Thank you, Dr. Bortz. It would be appropriate, I think, to have Dr. Blankenhorn's letter circulated by the Executive Secretary to all members of the Board of Regents, so that when this report is again made in Cleveland, we may consider some of its very important points."

DR. WALTER B. MARTIN: "Mr. President, I would like to go back to a point in connection with the Joint Commission on the Accreditation of Hospitals. I do not believe the Advisory Committee of that Commission is to be a policy making body, but purely an executive advisory body. The members of the Advisory Committee will include the Executive Officer of the American Medical Association, Dr. George F. Lull, the Executive Officer of the American College of Surgeons, Dr. Paul Hawley and the Executive Officer of the American Hospital Association. The present concept of the American Medical Association is that this is not a policy making body."

DR. WALTER L. PALMER: "I would like to make this additional comment. I am most concerned about where Dr. Sloan is going to have the greatest opportunity to be effective for the College. He has had more to do with this matter than any member of the College, and should be in a position to occupy the most influential position. In the meeting of the Executive Committee, I had the impression that we would give Dr. Sloan a greater opportunity to be of influence if he were on this Advisory Committee. We can't have Dr. Sloan in both places, or can we?"

PRESIDENT PINCOFFS: "I would like to ask Dr. Sloan to clarify the work of this Advisory Committee. I have the impression that while the Commissioners are the authority, the policy makers, they will meet rather infrequently, and that the actual effectuation of those policies will rest with the Advisory Committee and the Director, and that actually, therefore, the more strategic and important position in the actual conduct of affairs of these inspections and of the formulation of standard regulations will be that of the Advisory Committee. In other words, within the framework of the policies devised by the Commission, the Advisory Committee and the Director will actually conduct the affairs."

DR. ALEX. M. BURGESS: "I would like to add that a Commissioner cannot be on the Advisory Committee, although I have not seen anything in the setup of the Commission that makes that definite. Are you sure Dr. Sloan would not be eligible both as a Commissioner and as a member of the Advisory Committee?"

DR. LEROY H. SLOAN: "I thought we should be as intelligent on this whole situation as possible. (Through a series of lantern slides, Dr. Sloan presented the following facts.)

Name: Joint Commission on the Accreditation of Hospitals.
Address: 660 N. Rush St., Chicago, Ill.
Registered Agent: Dr. Paul R. Hawley, Chicago, Ill.

Organized exclusively for charitable, scientific, educational purposes; not for profit; not for propaganda purposes; not to influence legislation.

Corporate Members:

American College of Physicians
American College of Surgeons
American Hospital Association
American Medical Association

Purposes:

(1) To conduct inspection and accreditation programs;
(2) To establish standards for hospital operation;
(3) To recognize compliance with standards;
(4) To issue certificates of accreditation.

Board of Commissioners: To be made up of eighteen members, this number to be based upon the voting strength of each member organization. Commissioners shall be appointed to serve staggered terms of three years each.

Voting Power:

American College of Physicians 3
American College of Surgeons 3
American Hospital Association 6
American Medical Association 6

Should the Canadian Medical Association join the Commission, the number of votes would be increased to twenty, two being assigned to the Canadian Medical Association. Expenses of operation shall be commensurate with the number of votes of each organization.

Advisory Committee: To be made up of the chief administrative officer of each constituent organization.

Functions of Advisory Committee:

(1) Advisory to Board of Commissioners;
(2) Interpretation of work of Commission to their organizations;
(3) To recommend budgets;
(4) To determine number of hospitals to be inspected by constituent organization;
(5) To coördinate and consult on scheduling of inspections.

Director of Joint Commission: To be appointed by Board of Commissioners. Must be a physician with training in and knowledge of hospital administration.

Finances: Initial budget, $70,000.00 (A.C.P. share about $12,000.00); Reserve fund, $25,000.00 (A.C.P. share about $4,000.00).

Constituent organization to assume expenses of own inspection program. Total expenditure to depend on extent of inspection by each organization. Traveling expenses paid from budget of Joint Commission, not by constituent organization.

First Meeting, Board of Commissioners: 10:00 a.m., December 15–16, 1951, Drake Hotel, Chicago, Ill.

DR. SLOAN (commenting): "The constituent organizations assume expenses of their own inspection program. In other words, the American College of Surgeons will keep on with its work, the American Medical Association with its work, the American Hospital Association with its work, but every bit of their final report must be channeled through the Joint Commission. The American College of Physicians has never taken any part in accrediting hospitals, and, consequently, we have at the present moment no expenditures, except as may become incident to the expenditures necessary to carry on as a member of the Advisory Committee. We in the College are interested in professional care of the patient. The patient comes first and not the hospital, and unless this whole body recognizes that everything that is done in the hospital is directed toward the professional care of a patient, we might as well give up the program.

"The Director of the Commission will be appointed by the Board of Commissioners. The Board of Commissioners will meet occasionally, and when they meet everything they consider will have been channeled through the Advisory Committee. I think the key position is on that Advisory Committee and not on the Board of Commissioners.

"I believe members of the Board of Commissioners should be chosen near-by Chicago, thus to reduce expenditures. If the Commissioners are chosen from all parts of the country, the $70,000.00 budget will be exhausted in little time. The major expense will be cut down by the fact that our Advisory Committee, working in Chicago, will all be from Chicago. The Director is the most important man in the whole setup. He is required to be a physician and not a layman. He is expected to have training in and knowledge of hospital administration. The Director will be Chairman of the Advisory Committee and of the Board of Commissioners. Final approval of any hospital must be obtained finally through the Board of Commissioners."

DR. MARTIN: "I think the important position is on the Commission, and our strongest and ablest talent should be on the Commission. If we appoint our ablest representative on the Advisory Committee we tend to develop the idea that that body has authority which it does not and should not possess. We must further the idea that the Commission is the policy making body."

PRESIDENT PINCOFFS: "We will now proceed to the report of the Advisory Committee on Postgraduate Courses by Dr. Thomas M. McMillan, Chairman."

DR. THOMAS M. MCMILLAN: "During the spring of 1951 the College offered eight Postgraduate Courses, with a total registration of 505. During the autumn of 1951 it gave nine courses, which up to date have a registration of 608, but the registration is not yet complete, because two of the courses have not been given as yet. The total registration for the year 1951 already is over 1,100 and probably will approach 1,200. We try to keep before us the utter fallacy of judging the success of these courses by the numbers who attend them. We seek to find, as well as we can, the reaction of those who take the courses and to collect their suggestions for improvement. As far as we can judge, the courses given in 1951 have been quite successful. The Committee, in making recommendations to the Regents, constantly has in mind the importance and the desirability of discovering new directors and new institutions in which these courses may be given. Seven of the seventeen courses given during 1951 were given under new directors who had never given courses for the College before. We also keep before us the desirability of wide geographic distribution. During this year we have had three courses in the South, one in Atlanta, one in Galveston and one in New Orleans. We have also had a desire to get away

as far as possible from repeating courses each year by the same directors, and we are now at the point where we do not have to ask any director to give the same course year after year. There are perhaps two exceptions, and in the recommendations for new courses that I am about to recommend for the spring of 1952, there are one or two repeat courses—courses that were given in 1950, but there are rather special reasons for these.

"With the help of Dr. Bortz, representing the Committee on Educational Policy, we have decided to recommend to the Regents the following courses for the spring of 1952. I am not giving you, perhaps, the exact titles, but simply the broad titles:

1. GASTRO-ENTEROLOGY; University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.; Doctors Dwight L. Wilbur and Theodore L. Althausen, Co-Directors.
2. ALLERGY; Washington University School of Medicine, St. Louis, Mo.; Dr. Harry L. Alexander, Director.
3. DISEASES OF THE BLOOD VESSELS; Cornell University Medical College and the New York Hospital, New York, N. Y.; Dr. Irving S. Wright, Director.

"When this course was first given we felt there had been so much emphasis on the heart that we should remind our members and keep before them constantly the importance of thinking of the blood vessels as a part of the circulatory mechanism. Dr. Wright's course was really one of the outstanding courses we have had in recent years, and we thought after an interval of one year we might well repeat it.

4. HEMATOLOGY; Ohio State University College of Medicine, Columbus, Ohio; Dr. Charles A. Doan, Director.
5. INTERNAL MEDICINE; University of Michigan Medical School, Ann Arbor, Mich.; Dr. Cyrus C. Sturgis, Director.
6. INTERNAL MEDICINE; Hahnemann Medical College of Philadelphia and other institutions; Dr. Charles L. Brown, Director.

"Personally I am very pleased to recommend this course, because we have five medical schools in this city, and I have been personally very anxious to have all five of them give courses. This course will complete the roster of the five schools that have given courses within the last few years.

7. ELECTROCARDIOGRAPHY; Massachusetts General Hospital, Boston, Mass.; Dr. Conger Williams, Director.

"There still remains a great demand for courses in Electrocardiography. The course given last year by Dr. Gordon Myers in Detroit was one of the most successful courses we have had in recent years. Dr. Williams takes only a very small number, at the most twenty-five. It is a rather highly personal course and has always been most successful and well received, and since he does take such a small number of registrants and since we are not suggesting any other course in this subject, we thought we would like to recommend its repetition in the spring.

8. PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE; University of Toronto Faculty of Medicine, Toronto, Ont., Can.; Dr. Ray F. Farquharson, Director.

"As possible substitutes, to fill out our program of eight courses for the spring, we have held in reserve as possible substitutes in case any of the above courses cannot be scheduled the following:

1. RHEUMATIC DISEASES, under Dr. Walter Bauer in Boston, Mass.
2. INTERNAL MEDICINE, at the University of Colorado under Dr. Ward Darley.
3. INTERNAL MEDICINE, at the University of Southern California under Dr. Paul Starr.

"We have not approached Dr. Bauer and he might or might not be able to give such a course. We do know that Dr. Darley and Dr. Starr would be willing to give courses for the College.

"We are asking for your approval of these recommendations. It is a great help to us if we can have some preliminary approval of courses and directors from the Regents for future possible courses. In asking for this, I assure you that before they are actually scheduled, you will be consulted again, but if we can simply meet or by letter discuss various courses and have reasonable assurance that you approve of them, it will facilitate our work a great deal. Therefore, we are going to ask for approval in a broad sort of a way on several additional courses for the indefinite future. While we are looking for new courses and new directors, at the same time we feel that we should go back to certain old courses and old directors, when these have been very successful in the past.

1. HEMATOLOGY, by Dr. William Dameshek, Boston, Mass.
2. INTERNAL MEDICINE or HEMATOLOGY, at Salt Lake City under Dr. Maxwell M. Wintrobe.
3. GASTRO–ENTEROLOGY, at Philadelphia under Dr. Henry L. Bockus.
4. ALLERGY, at the Roosevelt Hospital, New York, N. Y., under Dr. Robert A. Cooke.
5. INTERNAL MEDICINE, at Pittsburgh, Pa., under Dr. Roy R. Snowden.
6. CARDIOVASCULAR DISEASES, at Philadelphia, Pa., under Dr. William G. Leaman.
7. INTERNAL MEDICINE, at Madison, Wis., under Doctors William S. Middleton and Karver L. Puestow.
8. CARDIOVASCULAR DISEASES, at the Michael Reese Hospital, Chicago, Ill., under Dr. Louis N. Katz.
9. INTERNAL MEDICINE, University of Oregon, under Dr. Howard P. Lewis.
10. CARDIOVASCULAR DISEASES, at the University of Southern California under Dr. George C. Griffith.
11. ELECTROCARDIOGRAPHY, at Detroit, Mich., under Dr. Gordon Myers.
12. ALLERGY, at Pittsburgh, Pa., under Dr. Leo H. Criep.
13. INTERNAL MEDICINE, at Philadelphia, Pa., under Dr. Garfield Duncan.
14. CARDIOVASCULAR DISEASES, at New York, N. Y., under Dr. Clarence E. de la Chapelle.
15. REHABILITATION, at New York, N. Y., under Dr. Howard Rusk.
16. CARDIOVASCULAR DISEASES or INTERNAL MEDICINE, at the Mayo Clinic, under Dr. Edgar V. Allen.
17. INTERNAL MEDICINE, at the University of California, under Dr. Stacy R. Mettier.
18. INTERNAL MEDICINE, at Cornell University, New York, N. Y., under Dr. David P. Barr.

"All the above courses have been given once or more previously. Now we have also in mind the following new courses to propose:

1. PSYCHOSOMATIC MEDICINE (under some other appropriate title), at New York, N. Y., under Doctors Harold G. Wolff and Stewart Wolf.
2. ELECTROCARDIOGRAPHY, at New York University under Dr. Charles E. Kossmann.
3. HEMATOLOGY, at Chicago, Ill., under representatives of three different schools, Dr. Howard L. Alt, Dr. Louis R. Limarzi and Dr. Leon O. Jacobson.
4. PSYCHOSOMATIC ASPECTS OF INTERNAL MEDICINE, at Topeka, Kans., under Dr. William C. Menninger.

5. *A course* under an appropriate title to be given at Chicago during November, 1952 immediately preceding the large Midwest Regional Meeting, this course under the direction of Dr. Frank B. Kelly.
6. PATHOLOGY and INTERNAL MEDICINE, possibly at Philadelphia under Dr. Baldwin Lucké.
7. CARDIOLOGY at Mt. Sinai Hospital, New York, N. Y., under Dr. Arthur M. Master.
8. INTERNAL MEDICINE, at Baltimore, Md., under Dr. Maurice C. Pincoffs.

"The only other suggestion has come to us from the registrants in a recent course. The suggestion was that in charging a registration fee of only $30.00 for these courses the College actually is not being realistic in these days when everything else, including the cost of printing, etc., has gone up so much. They have suggested that an appropriate fee would be $50.00, which is only $10.00 a day for five days. I simply bring it before you for any thought you may have on the matter."

PRESIDENT PINCOFFS: "Thank you, Dr. McMillan. This excellent report on one of the major functions of the College should be open first to discussion before we consider motions to give the approval that Dr. McMillan asked for."

DR. MARTIN: "I move that the report regarding recommention of courses be approved and that the Committee be authorized to complete their schedule from the suggestions made."

. . . The motion was seconded by Dr. Charles F. Moffatt. There was no discussion and the motion was put and carried. . . .

PRESIDENT PINCOFFS: "Although there is no recommendation concerning change in the registration fee, what is your advice? The Secretary points out that the fee of $30.00 is for members of the College only, and that non-members pay double. Therefore, if a motion were made to increase the registration fee of members to $50.00, it would also carry a fee of $100.00 to non-members."

. . . No motion was made to alter the current registration fees. . . .

PRESIDENT PINCOFFS: "May we have the report of the Committee on the Alfred Stengel Memorial Award, Dr. Reginald Fitz, Chairman?"

DR. REGINALD FITZ: "Mr. President and Regents, you will remember that the Alfred Stengel Memorial Award is a very special one, in brief, corresponding to the award of an honorary degree by the College to an individual because of his loyalty and service to the College, because of his outstanding influence in maintaining and advancing the best standards in medical education, practice and research and perpetuating the history and traditions of medicine and medical ethics in general and in upholding the dignity and efficiency of internal medicine in relation to public welfare. The Committee appointed this year to make nominations included the President, the Secretary-General and Doctors Ward Darley, T. Grier Miller, Robert Wilson, Jr., Benjamin F. Wolverton and myself. We gave considerable thought to this, and now wish to propose three candidates. The procedure is that we conduct a secret ballot and then the two candidates receiving the largest number of votes shall again be voted upon, and the candidate receiving the majority of votes then shall be the recipient."

. . . The Committee then placed in nomination three men who represented the kind of men they considered should receive the Award. Doctors J. Owsley Manier and Cyrus C. Sturgis were appointed as a Committee of Tellers to conduct a secret ballot, and one of the three nominees was selected and his name will be announced at the Convocation of the College at Cleveland during April, 1952. . . .

PRESIDENT PINCOFFS: "We shall now have the report of the Committee on Credentials, by Dr. Wallace M. Yater, Acting Chairman, in the absence of Dr. George Morris Piersol who is ill."

DR. WALLACE M. YATER: "The Committee met November 16 and 17 with Doctors Lathrope, Kinsman, McGee, Wilson and Yater in attendance, with Dr. Brower assisting in the place of the Chairman, Dr. Piersol, who is ill.

"The Committee reveiwed certain communications, which were largely for the special attention of the Committee itself and do not warrant reporting herein. However, one communication concerned the matter of the extension of the Associate term for current Associates who may be called to active military service. One communication revealed the attitude of the Department of the Army, which led the Committee to adoption of the following policy: if a member shall be on active duty out of this country, his case may receive favorable recommendation for extension of his Associate term for a period commensurate with that on foreign duty. If he be stationed in this country, the Committee sees no justification at the present time for extending his Associate term. We have assurances from the Surgeon General of the Army that it is a policy of that Office to facilitate the taking of the Board examinations by their Medical Officers.

"The Committee received three applications for the extension of Associate terms. They recommend for the approval of the Board of Regents the extension of the Associate term of Dr. Pierre C. Simonart, of Philadelphia, until the spring of 1953. The Committee does not recommend the extension of the Associate term of the other two applicants.

"The Committee reviewed the credentials of 179 candidates for Fellowship, and an analysis of the recommendations follows:

Candidates for FELLOWSHIP:

Recommended for Advancement to Fellowship	120	
Recommended for Election Directly to Fellowship	9	129
Recommended for Election first to Associateship		9
Deferred		31
Rejected		10
		179

"The Committee now moves the election of the following 129 candidates to Fellowship:" (The names are not herein listed, because they have already been published in the December, 1951 issue of this Journal.)

DR. YATER (continuing): "The Committee reviewed the credentials of 306 candidates for Associateship, and an analysis of its recommendations follows:

Candidates for ASSOCIATESHIP:

Recommended for Election	216	
Fellowship Candidates recommended for Election first to Associateship	9*	225
Deferred		70
Rejected		20
		306 plus *9

"The Committee recommends and I move the election of the following 225 candidates to Associateship in the College:" (The names are not herein listed, because they have already been published in the December, 1951 issue of this Journal.)

. . . By formal resolution those recommended by the Committee on Credentials for both Fellowship and Associateship were elected. . . .

DR. YATER (continuing): "Prepared for your attention is a set of duplicated sheets entitled 'Term of Associateship Expired, November 18, 1951.' The table referring to the class of Associates elected five years ago will have been altered by your action today, and thus the following is the proper analysis of what has happened to the 126 Associates elected five years ago:

Qualified for Fellowship	90
Deceased	4
Dropped for Delinquency	3
Resigned	11
Terms Extended by the Board of Regents	2
Dropped or Failed to Qualify	16
	126

"Additionally there are a group of miscellaneous Associates elected prior to October 20, 1946, whose terms were extended due to military service until the autumn of 1951. There were seven of these whose credentials were not found adequate by the Committee and eleven who made no attempt to present their credentials. Under terms of the By-Laws the following Associates must now be dropped from the College Roster because their maximal terms have expired." (A group of 34 Associates, named by Dr. Yater and spread on the Minutes, were officially dropped.)

DR. MARTIN: "May I bring up a matter now that has a bearing on the Credentials Committee report? I purposely did not bring it up before because I do not want to have any relation to any particular name, but to present it as a matter of policy. A number of men in the U. S. Public Health Service who were recommended for Fellowship or for Associateship brings up the matter of policy as to whether or not we take in men who are primarily administrators, rather than engaged in the clinical practice of medicine. Without giving names, No. 1 is primarily a hospital administrator and occupies a high position in the Service in Washington; he is not a clinical man. No. 2 in recent years has been a hospital administrator and presently is engaged in immigration and quarantine work and has had no strictly clinical work for many years. No. 3 has had some clinical work in psychiatry, though not in recent years; most of his work has been of an important and administrative character in Washington, and he is at present the Chief Quarantine Officer in one of our overseas stations. The point I raise for discussion is whether it is the policy of the College to make men of that type members of the College, or whether we should judge them strictly on the basis of whether they engage in clinical work in internal medicine."

DR. YATER: "We screen these candidates rather carefully. On the whole, I would say that we would not take a hospital administrator unless he had been in the past quite outstanding in the clinical field. Were the men to whom you referred up for Advancement to Fellowship or were they candidates for Associateship?"

DR. MARTIN: "One was up for Direct Fellowship and was degraded to Associateship; one was rejected and one was elected to Fellowship. The reason I brought this up is because we have a number of very capable men in internal medicine in the Public Health Service. To explain my interest in the matter, I have been consultant for the Public Health Service for many years. The matter came before me through some of our members who I know are excellent clinicians, and they feel a bit aggrieved that men who have no particular clinical qualifications, or who have never had much clinical experience, while unquestionably of a very high grade, are men of administrative capacities. I do not bring it up for or against any single man on this list, because they all have high qualifications in their particular field, but they

are not clinicians; they are not now and have not been for many years engaged in clinical work."

DR. BURGESS: "Mr. President, I would like to state that the Veterans Administration is in the same position. There are now a number of Managers of our Veterans Administration Hospitals who are Fellows of this College and are not doing clinical work. Some of these are certified by the American Board of Public Health and Preventive Medicine. They are excellent men, but I agree with Dr. Martin that this policy should be considered."

PRESIDENT PINCOFFS: "Unless the Regents wish to formalize their opinion in a motion, I would suggest that the President take action to forward an excerpt of the Minutes covering this discussion to each member of the Committee on Credentials, with the request that they consider it and suggest their policy in this matter at the next meeting of the Board of Regents."

DR. MARTIN: "Has not the Board some time in the past taken action on this matter?"

SECRETARY LOVELAND: "A long time ago the Committee on Credentials with the approval of the Regents established the precedent of not electing to membership in the College any one who is purely a hospital administrator and has no connections with clinical medicine. Now, in the Public Health Service and in the Veterans Administration there are many who when they were elected to the College were doing clinical work and later have developed into administrators. In observing the deliberations of the Credentials Committee yesterday, one of the candidates from the Public Health Service was denied membership because the Committee concluded he was purely a hospital administrator. I would remind you that the College does not limit its membership to internists. It recognizes Public Health and Preventive Medicine, and, naturally, the American Board of Public Health and Preventive Medicine. Therefore, candidates from this particular field have sometimes been elected even though now engaged primarily in administrative work. I think the policy is still not to encourage new candidates who are primarily in managerial positions."

DR. BURGESS: "I think there are many of the Veterans Administration members who were in clinical work when they entered the College as Associates, but had reached administrative positions before they came up for Fellowship."

DR. GEORGE H. LATHROPE: "Have not these men who are now in administrative work come up through the grind of a good deal of clinical work, and, if so, isn't that man entitled to membership from what he has done in the past, even though now he is in an administrative position? I would like to see this really clarified."

DR. MARTIN: "As far as a candidate who has been made an Associate and in the course of time comes up for Fellowship—a man who was a clinician and now is an administrator—is concerned, I see no reason why we should bar him from being advanced to Fellowship. For the selection of Associates, however, and for Direct Election to Fellowship from the ranks of those who for years have been engaged in administrative work and have no particular background of outstanding merit in clinical work, I raise this issue. I move that this question be given to the Credentials Committee for examination, to be reported on at the next meeting."

. . . The motion was seconded by Dr. Alex M. Burgess, put and carried. . . .

PRESIDENT PINCOFFS: "May we have the Treasurer's report by Dr. William D. Stroud?"

DR. WILLIAM D. STROUD: "The Committee on Finance will make recommendations concerning the investment of surplus funds not required for operation, and it will also report on security transactions since the last meeting of the Board. The present security holdings of the College are as follows:

	Book Value	*Market Value*	*Appreciation*
Endowment and Trust Funds	$374,618.18	$404,483.75	$29,865.57
General Fund	302,012.58	351,845.75	49,833.17
	$676,630.76	$756,329.50	$79,698.74

"The annual cash income from securities on our present holding basis is estimated by our investment counselor as $34,000.00, with an average yield of 4.53%. This compares with 4.58% for 1950; 4.2% for 1949. There is a possibility of slightly reduced rate of income, due to a reduction in common stock investments, and, likewise, the possibility of some reduction in rate of stock dividends, due to increased corporate taxation.

"We maintain close contact with our investment counselors, obtain regular analyses of our accounts and have the counselor meet with our Finance Committee at least once a year."

. . . Acceptance of the report was moved by Dr. Brower, seconded by Dr. Lathrope and duly carried. . . .

PRESIDENT PINCOFFS: "Now we shall have the report of the Committee on Masterships by Dr. Reginald Fitz, Chairman."

DR. FITZ: "Mr. President and members of the Board, this Committee is comprised of Dr. A. B. Brower, Dr. Stacy R. Mettier and myself. We are charged to bring in a nomination for proposed Master to the Board of Regents for election or rejection. The Committee moves that Dr. William S. Middleton be created a Master at the next Convocation."

. . . The motion was seconded by Dr. Wallace M. Yater, put and carried. . . .

PRESIDENT PINCOFFS: "May we now have the report of the Committee on Fellowships and Awards by Dr. Cyrus C. Sturgis, Chairman?"

DR. STURGIS: "The Committee on Fellowships and Awards met at the College Headquarters on November 16, 1951, with the following in attendance: Dr. Cyrus C. Sturgis, Chairman, Dr. T. Grier Miller, Dr. Walter L. Palmer, Dr. Wesley W. Spink, and with Dr. Philip E. Blackerby, Associate Director, International Division, W. K. Kellogg Foundation, Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell University, and Mr. E. R. Loveland, Executive Secretary.

The report of the Committee includes two meetings since the last meeting in St. Louis—the first meeting at Ann Arbor, Mich., on June 23, 1951, and the second meeting at the College Headquarters on November 16.

Latin-American Fellowship Program—At the meeting at Ann Arbor, with the following in attendance, Dr. Cyrus C. Sturgis, Chairman, Dr. T. Grier Miller, Dr. Walter L. Palmer, Dr. Douglas Donald (substituting for Dr. H. K. Detweiler), Dr. William C. Chaney (substituting for Dr. Wesley W. Spink), Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell University, Mr. E. R. Loveland, Executive Secretary, Dr. Benjamin G. Horning, Director, International Division and Dr. M. R. Kinde, Director, Division of Medicine and Public Health, and Dr. Emory Morris, Director, W. K. Kellogg Foundation, all candidates for the Latin-American Fellowships were reviewed and the following approved:

1. Dr. Jorge ARAUJO Grau, Bogota, Colombia, S. A.
2. Dr. Jose BARZELATTO Sanchez, Santiago, Chile, S. A.
3. Dr. Adolfo BISSO Zollner, Lima, Peru, S. A.
4. Dr. Alvaro CARBALLO Montero, San Jose, Costa Rica, C. A.
5. Dr. Jose Antonio GARCIA Reyes, Mexico, D. F.
6. Dr. Carlos HEINRICH Treuer, Concepcion, Chile, S. A.
7. Dr. Otto HERRMANN Koch, Santiago, Chile, S. A.

8. Dr. Arturo PINEDA Giraldo, Medellin, Colombia, S. A.
9. Dr. Jose M. PORTILLA, Quito, Ecuador, S. A.
10. Dr. Francisco RIVADENEYRA Hinojosa, Morelia, Mexico
11. Dr. Jose CARA, Cordoba, Argentina, S. A.

"The Committee then interviewed the following Latin-American Fellows who were on assignments at Ann Arbor, as follows:

1. Dr. Roberto Figueira SANTOS, Salvador, Bahia, Brazil, S. A.
2. Dr. Silvio Humberto RODAS Ortiz, Asuncion, Paraguay, S. A.,

and then reviewed the cases of Latin-American Fellowships previously awarded.

"Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell University, made a report concerning the Course, reviewing its organization and history.

"The Committee also reviewed the Research Fellowships of the College for the year 1950–51, and the Chairman also reported that the first recipient of the Brower Traveling Scholarship, Dr. Benjamin B. Wells, of Little Rock, Ark., had concluded pre-arranged visits to the University of Michigan Medical School and Hospital, Ann Arbor, to Ohio State University College of Medicine, Columbus, and to the University of Cincinnati College of Medicine at Cincinnati, and that a second field trip had been arranged to the University of Colorado School of Medicine and to the University of Utah School of Medicine.

"The Chairman then distributed a list of nominations that had been received from Regents and Governors of the College and from Professors of Medicine for the James D. Bruce Memorial Award for 1952. After general discussion of the list, it was so moved that Dr. James H. Gear, Deputy Director, South African Institute for Medical Research, Johannesburg, South Africa, be recommended to the Executive Committee of the Board of Regents as the Bruce Memorial Medalist for 1952; this motion was seconded and unanimously carried.

"In discussing Dr. Gear's candidacy it was stated that the National Foundation for Infantile Paralysis had agreed to pay the cost of the air passage, and that the University of Maryland, and several other institutions, had agreed to offer honoraria for his appearances before their organizations, if desired or required, thus assuring the American College of Physicians that it would be involved only in the $400.00 award and medal.

"Chairman Sturgis then distributed a list of nominations for the John Phillips Memorial Award for 1952 that had been received from the same source as the Bruce Award, and it was moved, seconded and unanimously carried that the nomination of Dr. Andre F. Cournand, New York, N. Y., be recommended to the Executive Committee of the Board of Regents as the John Phillips Memorial Medalist for 1952.

"Subsequently, both nominations were submitted to the Executive Committee of the Board of Regents and were unanimously approved.

"At this meeting the Committee also approved the announcement to be distributed to all Associates of the College concerning the A. Blaine Brower Traveling Scholarships (2) for 1952.

"This concludes the report of the meeting in Ann Arbor.

"The meeting on November 16 opened with a luncheon at the Penn Sheraton Hotel at 12:00 M., with Dr. Cyrus C. Sturgis, Chairman, Dr. Walter L. Palmer, Dr. Wesley W. Spink of the Committee, Dr. Philip E. Blackerby, of the Kellogg Foundation, Dr. E. Hugh Luckey, Director of the Orientation Course at Cornell, Dr. Maurice C. Pincoffs, President of the College and Mr. E. R. Loveland, Executive Secretary, in attendance, as well as the nine (9) current Latin-American Fellows presently pursuing the Orientation Course at Cornell. After the luncheon appropriate remarks were made by Chairman Sturgis, President Pincoffs, Dr. Blackerby, Dr. Luckey, and Mr. Loveland, after which the nine Latin-American Fellows were individually interviewed, as follows:

1. *Dr. Jorge ARAUJO Grau, Bogota, Colombia*

Specialty, Internal Medicine; presently enrolled in the Orientation Course at Cornell University. On December 1, 1951, he will report to the New York Hospital, under the preceptorships of Dr. E. Hugh Luckey and Dr. David P. Barr, for a period of one year. This is agreeable to his sponsors and to the Kellogg Foundation.

2. *Dr. Jose BARZELATTO Sanchez, Santiago, Chile*

Specialty, Internal Medicine; presently enrolled in the Orientation Course at Cornell University; on December 1, 1951, will report to Dr. Walter Bauer, Massachusetts General Hospital, to work under Dr. John E. Stanbury in the thyroid clinic for a period of one year.

3. *Dr. Adolfo BISSO Zollner, Lima, Peru*

Specialty, Endocrinology; presently enrolled in the Orientation Course at Cornell University. It had been previously proposed that he have one year of preceptorship or residency under Dr. Francis C. Wood at the University of Pennsylvania, but arrangements have not as yet been concluded, and the Executive Secretary has been instructed to have Dr. T. Grier Miller, as a member of the Committee, contact Dr. Wood to determine if the above program can be carried out for one year, beginning March 1, 1952, perhaps, as an assistant resident in the field of Endocrinology.

4. *Dr. Jose CARA, Cordoba, Argentina*

Specialty, Internal Medicine; presently enrolled in the Orientation Course at Cornell University. Chairman Sturgis is to contact Dr. Lawson Wilkins, Associate Professor of Pediatrics at Johns Hopkins University School of Medicine, to determine if Dr. Cara may work with him for one year in the field of Endocrinology in Children, beginning March 1, 1952.

5. *Dr. Alvaro CARBALLO Montero, San Jose, Costa Rica*

Specialty, Gastro-enterology; presently enrolled in the Orientation Course at Cornell University. Dr. Sturgis agreed to make arrangements with Dr. H. Marvin Pollard of the University of Michigan for Dr. Carballo to work on the Gastro-enterological service for one year, beginning March 1, 1952.

6. *Dr. Carlos HEINRICH Treuer, Concepcion, Chile*

Specialty, Cardiology; presently enrolled in the Orientation Course at Cornell University. Arrangements have been completed for Dr. Heinrich to work with Dr. Gordon B. Myers, Professor of Medicine at Wayne University, Detroit, for one year, beginning December 1, 1951.

7. *Dr. Otto HERRMANN Koch, Santiago, Chile*

Specialty, Vascular Diseases; presently enrolled in the Orientation Course at Cornell University. Arrangements have been completed with Dr. Irving S. Wright for Dr. Herrmann to work with him in the field of Peripheral Vascular Diseases for one year, beginning March 1, 1952.

8. *Dr. Arturo PINEDA Giraldo, Medellin, Colombia*

Specialty, Internal Medicine; presently enrolled in the Orientation Course at Cornell University. Dr. Walter L. Palmer, of the University of Chicago, has agreed to act as his preceptor at that institution for one year, beginning March 1, 1952.

9. *Dr. Francisco RIVADENEYRA Hinojosa, Morelia, Mexico*

Specialty, Internal Medicine; presently enrolled in the Orientation Course at Cornell University. Chairman Sturgis is to endeavor to arrange for him to work for one year at the Lahey Clinic, Boston, in the field of Gastro-enterology, and Dr. Lahey to name the preceptor. It was revealed that Dr. Rivadeneyra is Director of the

Regional Military Hospital in Morelia, and he feels that since there is such a great need for Army doctors in his country that he may not be able to finish the entire period of study planned for him here in the United States. If he is unable to finish, it will be because he is called involuntarily back to his country, as he has permission only to remain in the United States from 9–1–51 to 8–31–52; therefore, since he has only at present one year of leave with the Army, it may be that this assignment for him to work at the Lahey Clinic may be for only six months, but arrangements will be made for him to spend one year, beginning March 1, 1952. If arrangements cannot be completed at the Lahey Clinic, it was suggested that probably arrangements could be made for him at the Mayo Clinic, Rochester.

10. *Dr. Jose Antonio GARCIA Reyes, Mexico, D. F.*

Specialty, Internal Medicine; no Orientation Course; assigned directly under Dr. George W. Thorn, Peter Bent Brigham Hospital, Boston, for six months; November 1, 1951–May 1, 1952. Dr. Thorn advised that he reported on October 1. Dr. Blackerby, of the Kellogg Foundation, reported that Dr. Garcia would like an extension of his fellowship, and that the Foundation would be willing to provide for the extension from May 1, 1952, for six months, to work with Dr. Forsham at the University of California, to October 31, 1952. The Committee approved the extension.

11. *Dr. Jose M. PORTILLA, Quito, Ecuador*

Specialty, Nutrition; originally assigned to start Orientation Course at Cornell University on November 1, 1951, for six months, but will be delayed in reporting, due to unavailability of necessary local funds.

"The following six (6) Latin-American Fellows have completed their work and returned home, and will receive appropriate Certificates, signed by their preceptors:

1. *Dr. Henrique BENAIM Pinto, Caracas, Venezuela*

Formal reports received from Doctors Blumgart and Wolff; certificate signed by Dr. Herrman L. Blumgart, preceptor; issued under date of November 16, 1951, for period October 1, 1949, to July 14, 1951.

2. *Dr. Rodolfo DE CASTRO Curti, Mexico, D. F.*

Preceptor's report filed; certificate issued under date of November 16, 1951, for period September 1, 1949, to May 2, 1951, and signed by Dr. Cyrus C. Sturgis, preceptor.

3. *Dr. Bruno GUNTHER Schaffeld, Concepcion, Chile*

Preceptor's final report filed; certificate issued under date of November 16, 1951, for period September 20, 1950, to July 30, 1951, and signed by Dr. Eugene M. Landis, preceptor.

4. *Dr. Horacio JINICH Brook, Mexico, D. F.*

Final report of preceptor filed; certificate issued under date of November 16, 1951, for period September 1, 1949, to July 15, 1951, and signed by Dr. David P. Barr, preceptor.

5. *Dr. Francisco LICHTENBERG Schneider, Mexico, D. F.*

Final report of preceptor filed; certificate issued under date of November 16, 1951, for period January 14, 1950, to May 13, 1951, and signed by Dr. Paul Klemperer and Dr. Arthur P. Stout, preceptors.

6. *Dr. Jacques TREMBLAY, Montreal, Que.*

Preceptor's report filed; certificate issued under date of November 16, 1951, for period November 1, 1949, to May 29, 1951, and signed by Dr. Henry L. Bockus, preceptor.

"The Executive Secretary displayed a sample of the certificate which is issued to these Latin-American Fellows upon the completion of their work, and the Committee suggested certain minor changes, and also requested that in the future the certificates be prepared long enough in advance so that the preceptor may sign same, together with his title, and present same in person to the Latin-American Fellow immediately upon the completion of his work.

"The following Latin-American Fellows are still working in the institutions to which they were previously assigned by the Committee, and satisfactory interim reports have been received concerning their activities:

1. *Dr. Guido BATTILANA Dasso, Lima, Peru*

Specialty, Internal Medicine; working on service of Dr. George W. Thorn and preceptorship of Dr. Eugene C. Eppinger, Peter Bent Brigham Hospital, Boston, since March 1, 1951; work will be concluded on February 28, 1952.

2. *Dr. Fructuoso BIEL Cascante, Concepcion, Chile*

Specialty, Gastro-enterology; working under Dr. Thomas E. Machella, University of Pennsylvania Hospital, Philadelphia, 3–15–51 to 3–1–52. Inasmuch as Dr. Biel is working in Philadelphia he attended the luncheon and the Committee also interviewed him.

3. *Dr. Luiz Carlos DE BARROS, Sao Paulo, Brazil*

Specialty, Cardiology; failed to accept fellowship under Dr. Edgar V. Allen, preceptor, 3–2–51, and returned to his home; fellowship cancelled and no certificate to be issued.

4. *Dr. Aloysio de Salles FONSECA, Rio de Janeiro, Brazil*

Specialty, Hematology; working under Dr. Cyrus C. Sturgis, preceptor, 6–29–51 to 6–29–52.

5. *Dr. Egon LICHTENBERGER Salomon, Bogota, Colombia*

Specialty, Pathology; fellowship under Dr. Paul Klemperer, Mount Sinai Hospital, New York, N. Y., 1–1–51 to 1–1–52.

6. *Dr. Jorge MAISTERRENA Fernandez, Mexico, D. F.*

Specialty, Endocrinology; four months, 1–20–51 to 5–21–51, under Dr. George W. Thorn, Peter Bent Brigham Hospital, Boston, then transferred to Dr. James H. Means, Massachusetts General Hospital, Boston, in field of radioactive iodine; fellowship originally scheduled to carry through 1–20–52, but Dr. Maisterrena has applied for an extension of his fellowship to 7–1–52, and the Committee recommended the extension of this fellowship to July, 1, 1952, and the Kellogg Foundation so approved.

7. *Dr. Hecter ORREGO Matte, Santiago, Chile*

Specialty, Gastro-enterology; under preceptorship of Dr. Henry L. Bockus, University of Pennsylvania Graduate School of Medicine, Philadelphia, 9–15–50 to 6–1–51; then under preceptorship of Dr. Cecil J. Watson, University of Minnesota, 6–15–51 to 12–15–51. Dr. Orrego applied to the Kellogg Foundation for an extension of two months, to 2–15–52, with Dr. Watson, and it was moved, seconded and approved, both by the Committee and the Kellogg Foundation.

8. *Dr. Ruy PEREZ TAMAYO, Mexico, D. F.*

Specialty, Pathology; working under preceptorship of Dr. Robert A. Moore, Washington University School of Medicine, St. Louis, 9–20–50, for one year, and then assigned to Dr. Lauren Ackerman, Barnes Hospital, St. Louis, 9–20–51 to 4–1–52.

9. *Dr. Valdir Cordeiro PESSOA, Recife, Brazil*

Specialty, Physiology; working under Dr. A. C. Ivy, preceptor, University of Illinois College of Medicine, 9–13–50 to 2–22–51, when, due to serious illness of his father, he returned to Brazil, and thereafter returned on 9–8–51. It was revealed that Dr. Pessoa is working for his Master's degree and he is anxious to obtain some clinical work. Arrangements will be made so that he can attend Dr. Walter L. Palmer's seminars at the University of Chicago, and it was voted to give him an extension of time long enough to complete his program for his Master's degree, until the end of the academic year. Therefore, his fellowship has been extended from March 1, 1952, to the end of the academic year, probably in June. Dr. Blackerby of the Kellogg Foundation will advise his present preceptor of the above.

10. *Dr. Silvio Humberto RODAS Ortiz, Asuncion, Paraguay*

Specialty, Cardiology; working under Dr. Franklin D. Johnston, preceptor, Heart Station, University of Michigan, 5–15–51 to 12–31–51, after having completed Dr. Louis Wolff's postgraduate course in cardiology, 2–29–51 to 5–12–51.

11. *Dr. Roberto Figueira SANTOS, Salvador, Brazil*

Specialty, Internal Medicine; working under Dr. Cyrus C. Sturgis, preceptor, University of Michigan, 3–1–51 to 3–1–52. It was recommended and approved by the Committee that Dr. Santos be permitted to spend two years in the United States, to 9–1–52, in which the Kellogg Foundation concurred. Dr. Sturgis will arrange program for the extension granted.

"This concludes our report so far as the Latin-American Fellows are concerned.

"*A.C.P. Research Fellowships*—The Committee reports that five of the six 1950–51 Research Fellows concluded their work, and that the Committee received from each candidate a detailed report on the work accomplished and manuscripts or publications emanating therefrom. Certificates have been issued to them, signed by the proper Officers of the College and their preceptors. The Chairman wishes to state that highly satisfactory reports were received from the preceptors.

"You will recall that one Research Fellow began his fellowship July 1, 1950, worked through October 11, 1950, when he had to withdraw, due to active service with the U. S. Navy; the balance of his award ($2,161.29) is being held for his resumption of the fellowship later, as previously approved by the Board of Regents.

"The following three (3) Research Fellows, 1951–52, were unable to accept their awards, due to call to active military service:

1. *Dr. John William Athens*

$3,500.00; to work at Johns Hopkins Hospital, under Dr. F. W. Barnes, Jr., preceptor; field, protein regeneration.

2. *Dr. Sidney Harold Ingbar*

$3,500.00; to work at Thorndike Memorial Laboratory, under Dr. Maxwell Finland, preceptor; field, metabolic physiology of infection.

3. *Dr. James Edwin Wood, III*

$3,500.00; to work at Evans Memorial, Massachusetts Memorial Hospitals, under Dr. Robert W. Wilkins, preceptor; field, circulation in the extremities.

"The Committee recommends that the grants made to these three (3) Fellows be held in reserve until they have completed their military duty and are available to carry out the original terms of the grant."

. . . On motion by Dr. Cyrus C. Sturgis, duly seconded, put and carried, this recommendation was approved. . . .

DR. STURGIS (continuing): "The Committee desires to report that the following 1951–52 Research Fellows started work on schedule, July 1, 1951:

1. *Dr. Amoz Immanuel Chernoff*

$3,000.00; Department of Hematology, Washington University School of Medicine, under Dr. Carl V. Moore, preceptor; field, hemolytic anemias.

2. *Dr. John William Harris* (Alfred Stengel Research Fellow)

$3,500.00; Thorndike Memorial Laboratory, Boston City Hospital, under Dr. William B. Castle; field, hematology.

3. *Dr. John Edmund Kiley*

$3,500.00; Albany Medical College, under Dr. A. V. Wolf and Dr. William B. Deichmann, preceptors; field, renal diseases.

"From a list of nine (9) applicants for the Research Fellowships for 1952–53, the following were selected:

1. *Calvin Ezrin;* 25; a graduate of the University of Toronto School of Medicine, 1949; to work under Dr. Ray F. Farquharson, Department of Medicine, University of Toronto, Toronto, Ont., to study the effect of severe malnutrition from various causes on endocrine structure and functions, $4,000.00.

2. *Thomas William Fyles;* 26; a graduate of the University of Manitoba Faculty of Medicine, 1949; to work under Dr. Bram Rose, McGill University Clinic, Royal Victoria Hospital, Montreal, Que., to study the effect of ACTH and Cortisone on asthma; $3,000.00.

3. *Ladd Watts Hamrick, Jr.; 28*; a graduate of the Bowman Gray School of Medicine, 1946; to work under Dr. J. D. Myers, Department of Medicine, Duke Hospital, Durham, N. C., in the field of splanchnic blood flow and metabolism; $3,000.00.

4. *Avard Marion Mitchell; 32*; a graduate of Harvard Medical School, 1950; to work under Dr. Samuel A. Levine, Peter Bent Brigham Hospital, Boston, in the clinical study of cardiovascular diseases; $3,000.00.

"The following candidate, *Dr. Calvin Ezrin*, was selected from the above group of four to be designated as the 'Alfred Stengel Research Fellow,' on account of his outstanding qualifications.

"The above calls for a total appropriation of $13,000.00."

. . . At this point, Dr. Cyrus C. Sturgis moved the approval of the Research Fellowship Awards as recommended and the appropriation of $13,000.00. The motion was seconded by Dr. Charles F. Moffatt, put and duly carried. . . .

DR. STURGIS (continuing): "The Committee considered recommending an increase of the Research Fellowship grants from the present stipends of $3,000.00 for unmarried candidates, $3,500.00 for married candidates and $500.00 additional for the Alfred Stengel Research Fellow. After considerable discussion, it was decided, however, to request the Executive Secretary to gather information about the size of other Research Fellowship grants, and then consider this problem at a later meeting of the Committee.

"The Committee considered the thirty-seven (37) applications for the A. Blaine Brower Traveling Scholarships—two (2), amounting to $400.00 each—and unanimously selected from these *Dr. William H. Bates,* of Cottonwood, Ariz., as the first recipient and *Dr. Donald Harvey Labby,* of Portland, Ore., as the second recipient for 1952."

. . .Dr. Cyrus C. Sturgis at this point moved the approval of the Brower Scholarships as recommended. The motion was seconded, put and carried. . . .

DR. STURGIS (continuing): "Dr. Benjamin B. Wells, of Little Rock, Ark., was the first recipient of the A. Blaine Brower Traveling Scholarship, 1951, and his activities, as directed by the Committee, were as follows: In June, 1951, he spent one week at the University of Michigan, inspecting the Department of Medicine and arranging plans with the Chairman of the Committee for further visits elsewhere. He was then sent for several days to Ohio State University, Columbus, where Dr. Charles A. Doan, Dean, directed his activities; from there he went to the University of Cincinnati, and was supervised in his visit while there by Dr. Marion A. Blankenhorn, Professor of Medicine; in the autumn he spent one week at the University of Wisconsin, where arrangements had been made with Dr. William S. Middleton, Dean. Arrangements are now being made for him to spend one week at the University of Utah, with Dr. Maxwell M. Wintrobe, Professor of Medicine, Salt Lake City.

"Dr. Wells has been exceedingly pleased to be the first recipient of this Traveling Scholarship, and in a letter to the Chairman he expressed his sincere appreciation for it and for the arrangements which were made for his visits to various medical institutions."

PRESIDENT PINCOFFS: "I think we should approve that report as a whole. I am sure I express the Regents' appreciation of the tremendous amount of work that is accomplished by this Committee and for the very personal interest it takes in all of these men who are recipients of these fellowships."

. . . It was moved by Dr. George H. Lathrope, seconded by Dr. Wallace M. Yater, put and carried, that the report be accepted as a whole. . . .

PRESIDENT PINCOFFS: "Dr. Alex. M. Burgess, Chairman, will kindly present the report for the Committee on the ANNALS OF INTERNAL MEDICINE."

DR. BURGESS: "Your Committee met on Saturday, November 18, 1951. There were present Doctors Palmer and Burgess. Conferences were held with Mr. David A. Horn, an Executive Assistant of the College in charge of advertising. The Editor, being also President of the College, was unable to attend the meeting, although certain of the matters considered by the Committee were discussed with him before the meeting.

"1. *Cost Analyses and Circulation Comparisons:* A summary of the figures relating to these topics was received from the Executive Secretary and is attached to this report (attachment A). Further discussion will be found on the typed 'Agenda' of this meeting (attachment B), paragraph 1. These data show a substantial increase in income both from subscriptions and from advertisements, great enough in fact to compensate so completely for the greater cost of printing and publishing the ANNALS that the surplus of over $58,000.00 resulted, which was almost the same as that of the previous year (just under $60,000.00). This, in the judgment of the Committee, is very favorable and further reference to it will be made in paragraph 10 below.

"2. *The Publication of a Part II Edition,* limited to 'The Acute Radiation Syndrome': Contract for this publication is a fait accompli. Your Committee adds its full approval. The matter of whether advertisements should or should not be carried in this supplementary publication should, in the judgment of the Committee, be left to the Editor and the managerial staff.

"3. *Increased Costs and Financial Data:* Your Committee notes that increased postage costs are to be anticipated during the coming year and that certain salary increases are also planned. It further notes that a correspondingly increased budget will cover these items and that an estimated increase in income should result in a surplus of about the same magnitude as that of the past two years.

"4. *Report of the Editor:* As noted above (paragraph 1) the Editor was not able to attend the meeting and present a report.

"5. *Reduced Subscription Rate for Medical Students, Interns and Bona fide Residents:* This matter was discussed, and your Committee voted to recommend that

the ANNALS be made available to individuals in these three categories at the same rate charged to dues-waived members of the College ($7.00). (Recommendation No. 1.)

"6. *Communication from Dr. Gordon McHardy,* with answer by Editor Pincoffs: This correspondence may be summarized by saying that Dr. McHardy wrote to inquire whether or not it would be proper for the proceedings of the postgraduate course in gastro-enterology given by him and others, some of whom are not members of the College, to be published as a Symposium in the American Practitioner and Digest of Treatment, as desired by the Editor of that publication. Dr. McHardy indicated that credit would be given to the College should this be done. Dr. Pincoffs expressed the opinion that the ANNALS has no particular right to these proceedings and that the lecturers in the course should be free to submit their material wherever they choose. He further indicated that limitation of space would probably not permit the publication of many of those papers in the ANNALS, if they were submitted to him. (Recommendation No. 2.)

"7. *Delays in Publication and Action:* (*a*) *Publication of the* ANNALS *late in the month:* It was called to the attention of your Committee that the ANNALS usually appears well after the 15th of the month, the date on which its delivery to its subscribers is intended. Your Committee realizes that the appearance of a journal on the first day of each month makes it much more satisfactory to advertisers. Such a prompt appearance is also very satisfactory to subscribers. It is noted that certain other medical publications are able to achieve this promptness of publication. It is, therefore, the opinion of your Committee that although such in ideal cannot, of course, be attained at once, every effort should be made to reach it by gradually advancing the date of publication in each month, until it has been attained. (Recommendation No. 3.)

(*b*) *Delays in Acceptance or Rejection of Manuscripts:* A delay of several months in the acceptance or rejection of manuscripts is a considerable hardship to an author who will, if his contribution is rejected, naturally wish to submit it elsewhere. In the judgment of your Committee, it would be wise for the College to employ at least two qualified young internists to assist in the work of reading manuscripts. This matter has been discussed informally with the Editor and has his approval. He further stated that such young physicians could well be considered as in training for future editorship. (Recommendation No. 4.)

(*c*) *Delay in Publication of Accepted Articles:* As noted in the report of the Committee on the ANNALS of last year, the Editor was authorized to increase the number of original articles and case reports. Table I shows the average delay in publication of original articles and case reports from February to October, 1951, inclusive. There is also shown the number of pages devoted to these two types of communications in each month. It will be noted that the delay as regards the publication of original articles has been materially reduced (to 9.6 months in the October issue), but that there has been no appreciable improvement in regard to case reports as yet.

TABLE I

	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.
Articles	18.6	18	20	19.7	14.9	14	10	10	9.6
Case Reports	25	23.6	15	20.5	23.8	22.2	24.3	20.8	18
Pages	206	250	217	187	190	247	161	248	175

Average delay between the date of receipt for publication and publication of articles and case reports by months, February to October, 1951, incl. The third column gives the number of pages of scientific material of these two types in each issue.

The Committee also reports that a letter expressing some criticism of the ANNALS, because of this delay, has been received from a Fellow of the College. In the judgment of your Committee, the progress that has been made is commendable, and it seems reasonable to hope that further progress can be achieved by a continuation of the inclusion of an added number of communications until a still better result has been attained. (Recommendation No. 5.)

"8. *Halftone Reproductions:* It was suggested to your Committee that some of the reproductions, especially x-ray films, could be improved if more expensive paper were used. In the judgment of this Committee it would be well to investigate this further, as it believes that poor reproductions are the mark of a poor journal, and that the ANNALS should be without a superior in its field. (Recommendation No. 6.)

"9. *Format Changes:* In the opinion of your Committee the ANNALS presents a drab exterior. The fine print of the Table of Contents on putty colored paper cannot be considered beautiful. It would be well, your Committee believes, to consider changes; your Committee not attempting to suggest a definite solution of this problem, ventures to express the opinion that, for example, a dark green cover with gold lettering and the Seal of the College (green and gold are the official colors of the College), and the relegation of the Table of Contents to the first page of the advertising section, opposite the inside of the cover, would be an example of a worth while improvement in the appearance of our journal. (Recommendation No. 7.)

"10. *General Policy Regarding the* ANNALS: With the substantial surplus earned by the ANNALS during the past two years and anticipated in 1952, your Committee can see no reason for any hesitation on the part of the College in applying a larger part of this money to improving the ANNALS. Many of the suggestions made in this report involve increased costs. Is not that what this money is for? Will not an improved ANNALS not only reflect credit on the College, but eventually increase its own prosperity? May your Committee call to your attention the quotation with which our President of a year ago concluded his memorable address: 'Make no small plans, they have no magic to stir men's souls.'

Recommendations: On the basis of the opinions expressed in this report, and with due humility and deep appreciation of the great achievements of the Editor and his staff in having made the ANNALS the outstanding journal that it is, the following recommendations are presented:

1. It is recommended that the ANNALS be sent to medical students, interns and bona fide residents at the same rate charged to dues-waived members of the College (present rate, $7.00).

2. It is recommended that Dr. McHardy be notified that the College recognizes no obligation on the part of participants in postgraduate courses to submit their material to the ANNALS, and can see no objection to the publication of that material in any reputable journal, with credit being given to the College for sponsorship of the course.

3. It is recommended that every effort be made to advance the date of the delivery of the journal to its subscribers each month until publication on the first day of the month is achieved.

4. It is recommended that an attempt be made to secure the services of two properly qualified young internists to help in reading manuscripts, and to be trained in editorial work as the Editor may see fit to train them, with the details of their employment and training to be left to the Editor and the management of the ANNALS.

5. It is recommended that the Editor be authorized to continue the publication of additional original articles and case reports as he has been doing to the extent that may be necessary to further reduce the delay between the receipt of publication and the publication date.

6. It is recommended that further study be given to the matter of improving the halftone reproductions in the ANNALS, with the idea that real improvement would justify a considerable increase in the cost of such reproductions.

7. It is recommended that the matter of a change in the format of the ANNALS be studied by the Editor and Executive Staff, in the hope of improving its appearance.

8. It is recommended that a general policy of using a larger proportion of the surplus than has hitherto been so used, for the purpose of improving the ANNALS not only in the matters suggested in the above recommendations, but also in such other ways as may be found appropriate, with the idea that the ANNALS, if made even more acceptable in the eyes of subscribers, contributors and advertisers than it is at the present time, will in turn inevitably be not only more satisfactory, but more profitable —and thus will be established a circle that is anything but vicious."

PRESIDENT PINCOFFS: "Before we take action on this report, the next item on the agenda is the report of the Editor, which is merely to the effect that he thanks this Committee on the ANNALS for its careful and helpful survey. I think that the College must look forward to the time when its two aging Editors transfer their responsibilities. This lies in the hands of the Regents. I do believe that some of the difficulties in getting out the journal on time and some of the delay in making decisions about manuscripts can be attributed to the rather limited staff of the ANNALS and the very overwhelming number of papers that are received.

"I will now ask you to consider what you would like to do with the report of the Committee on the ANNALS. There are a number of recommendations, some of which do not need specific motions, other than approval of the report as a whole. One recommendation, the addition to the staff of the Annals, is a matter which should be dealt with separately and, if I may suggest, probably not hurriedly on this occasion. The budget for the ANNALS for 1952 is already in. It can be amended, but it also could be amended at our spring meeting, and if that meets with the approval of the Regents, unless they wish to take action now, it would be my suggestion that something concrete in the terms of a budgetary amendment to provide for such additional assistance be submitted, together with the names of the potential assistants, through the Committee on the ANNALS by the Editor at the next meeting in Cleveland, there to be dealt with by the Regents."

DR. YATER: "Mr. President, I can see no reason to take these items up separately. They all sound good to me, and I move that we accept the report as a whole, including your suggestion to leave the one matter to our Cleveland meeting."

. . . The motion was seconded and opened for discussion. . . .

MR. LOVELAND: "To change our paper stock from the present fairly good grade of English finish paper to coated paper, it would increase the cost by several thousand dollars annually. I have already investigated that on one or two occasions, the last time six months ago."

DR. YATER: "If we use coated paper only for illustrations, that would reduce the increased cost."

MR. LOVELAND: "That is true, but it would be probably impractical to tip in the illustrations, but to use the coated paper for complete signatures where many illustrations are concerned."

DR. BURGESS: "That recommendation was for further study of this subject. It was not for decision at this point."

DR. FITZ: "I think the recommendations are very interesting, but it seems to me as you hear them read they introduce a great many complications, not only from the point of view of costs, but from the point of view of other matters. If Dr. Yater would be willing, I would like to suggest that any action on this report be delayed for further study and be again reported at the next meeting. I would rather wait and get more information."

DR. BURGESS: "You may notice the way the recommendations were worded that acceptance of the report, as moved by Dr. Yater, does not commit us to any of these decisions. It merely commits us to take up all these topics for consideration as the Committee has suggested."

DR. YATER: "I would like to amend my motion to read 'that we accept the report in principle as a whole, leaving the matter of additional editorial assistants and budgetary provisions, therefore, for more specific report at the Cleveland meeting.'" . . . The seconder accepted the amendment; the motion was put and carried. . . .

PRESIDENT PINCOFFS: "Will Dr. LeRoy H. Sloan now report on the Conference Committee on Graduate Training in Medicine?"

DR. SLOAN: "This Committee held a meeting in Atlantic City during the last Annual Session of the American Medical Association. All members were present, except Dr. Alex. M. Burgess. We cleared the decks of a large number of cases of hospitals that were up for consideration with regard to approved residency training. At the end of the meeting, I think all of us felt that for the first time there had been a pretty good solution to most of the problems that were presented.

"The mechanism of this Committee's work is that all hospital approvals come first to the Council on Medical Education of the American Medical Association, where they are filtered, screened, and those that are up for discussion or further consideration are referred to the local Conference Committee, consisting of Dr. Walter L. Palmer and myself. We individually send back a report, which is combined with the report of the American Medical Association. Then if the Committee still questions the approval or disapproval of a hospital, those applications are then considered by the whole Conference Committee. I feel that this Conference Committee accomplishes a great deal. Of course, it has no significant position or legal status, but it certainly does help to support the general movement for the proper approval of institutions that are doing graduate work."

PRESIDENT PINCOFFS: "I will ask Dr. LeRoy H. Sloan now to continue with the report of the Committee on Public Relations."

DR. SLOAN: "A meeting of the Committee on Public Relations was held on Saturday, November 17, 1951, at the College Headquarters, with Doctors Edward L. Bortz, Dwight L. Wilbur, LeRoy H. Sloan present, and Dr. Maurice C. Pincoffs, ex officio.

"I. *Communications:*

(a) It was the sense of the Committee that the Executive Secretary express the opinion for the Board of Regents to Dr. Page that his appearance would not, at this particular time, serve any significant purpose since the policy of the American College of Physicians prevents action on matters of this particular nature. We have, as you know, no political policy committee, and it was not felt that the College should enter into a discussion of the particular Bills referred to in Dr. Page's communication; although the Committee accepts in principle the necessity for improving federal medical services.

(b) A communication was received from the National Midcentury Committee for Children and Youth, which is acknowledged. No action taken.

(c) A portion of the correspondence from the National Research Council Committee on Cancer Diagnosis and Therapy was not available at the time of our meeting.

(d) A communication was received from the National Conference on Christians and Jews relative to a cash donation to the Library of the Berlin Free University. The Committee suggests that the American College of Physicians supply two complimentary subscriptions of the Annals of Internal Medicine to this Library.

(e) A communication was received from Doctors William S. Middleton and James J. Waring relative to changes in the Fellowship Pledge. The President is requested to appoint a special committee of the Secretary-General, the two past Marshals and the present Marshal to consider and report on recommendations relative to these changes.

"II. The Committee received a request from Wyeth, Incorporated, to cover the 1952 Annual Session by highlight sound motion picture.

"The Committee renders no report, but it feels that you all were exposed last night to the excellent presentation of the film from the St. Louis Meeting and may have your own reactions.

"III. A waiver of dues is recommended for Dr. Edward J. Wannamaker until he is able to resume remunerative work.

"IV. We recommend the acceptance of the resignations of all the applications for resignations, as follows:

Fellow

Swanson, Clifford A., M.C., U. S. Navy

Associates

Arms, Arnold V., Kansas City, Mo.
Brackley, Joseph E., Bakersfield, Calif.
Cate, Randolph A., Nashville, Tenn.
Corrado, Albert G., Richland, Wash.
Crumrine, Clarence A., Washington, Pa.
Henry, Blondy S., Russellville, Ala.
Issos, Demetrios N., Birmingham, Ala.
Moss, John E., Mobile, Ala.
Parker, Andrew James, Lewistown, Pa.
Phelps, James E., Paterson, N. J.
Sandella, Joseph F., New Brunswick, N. J.
Stone, Frederick J., Buffalo, N. Y.
Taylor, Elizabeth A., Fort Worth, Tex.
Thomas, Morris C., Waukesha, Wis.
Thomas, Sydney F., Palo Alto, Calif.
Zolov, Benjamin, Portland, Maine

"Most of the resignations from Associates came as the result of their having been unable to fulfill the requirements for advancement to Fellowship within the maximal five-year term allowed by the By-Laws, and they preferred to resign rather than to be dropped."

PRESIDENT PINCOFFS: "The first matter in this report requiring action is the recommendation of furnishing two free subscriptions to the Library of the Berlin Free University."

. . . Motion was duly made and seconded and carried, approving this recommendation. . . .

PRESIDENT PINCOFFS: "The next item requiring action is the recommendation for the appointment by the President of a special committee to study the suggested alterations in the Fellowship Pledge and to make a report back to the Regents."

. . . On motion by Dr. Cyrus C. Sturgis, seconded by Dr. A. B. Brower, put and carried, this recommendation was approved. . . .

PRESIDENT PINCOFFS: "The next item on which there should be official approval is the recommendation concerning the waiver of dues of Dr. Edward J. Wannamaker, and the acceptance of the resignations of the sixteen Associates and one Fellow."

. . . On motion by Dr. Wallace M. Yater, seconded by Dr. Walter L. Palmer, put and carried, the recommendations of the Committee were approved. . . .

PRESIDENT PINCOFFS: "In regard to the Tele-Clinic Moving Picture of the Cleveland Session, it has been pointed out that these serve a distinct historical value when filed in our Archives, and they have created favorable comment when shown at Regional and other meetings. Their disadvantage, as I see it, is that there is a certain amount of diversion of interest during meetings when bright lights are cast around on the audience, on the speaker and so on, and there appears to be a certain aura of advertising. It was felt that this matter should be discussed by the Regents and their decision followed. I question whether this will be a permanent matter. Wyeth has already withdrawn, I understand, from making a sound motion picture for a number of other associations, but continues this year only with a limited few, including the American Medical Association and the College."

DR. STURGIS: "I am interested in this for two reasons. It is of some importance as a historical record, but far more than that, I thought the five-minute presentations were quite worth while. Any one could listen to these very profitably. My criticism is that these presentations were only five-minute résumés of the entire speeches, and the speakers all galloped through them rather hurriedly. Some one ought to meet with the individuals selected for these presentations and make a few helpful suggestions. I am going to show the film before our Journal Club. It has some very good presentations that I think should be heard, and it is a method of teaching that I think is worth while for pointing the way. I, too, am annoyed by the lights and all that sort of business, but that is not too important, and I would like to move that we continue this film at least for another year."

. . . The motion was seconded and opened for discussion. . . .

. . . Dr. Wallace M. Yater suggested that there be a committee appointed to confer with the technicians as to what shall be recorded. Mr. Loveland explained that the content of the picture from St. Louis was selected by Dr. William S. Middleton, as President of the College, and not by Wyeth. The technicians worked very closely with Dr. Middleton and the General Chairman, and followed their advice and directions explicitly. . . .

. . . The motion was then put and carried. . . .

PRESIDENT PINCOFFS: "I would like to ask, since the responsibility may fall on me, whether some one would volunteer some advice as to whether to increase the part of the film that deals with five-minute presentations at the expense, perhaps, of the Convocation and other ceremonials?"

DR. WALTER L. PALMER: "The members of Journal Clubs are not interested much in the Convocation."

DR. STURGIS: "I would rather see less pageantry and more speeches, but enough of the ceremonials for historical purposes."

MR. LOVELAND: "We have had criticisms both ways. At the Regional Meetings at which the film has been shown, often at the Banquet where the audience is supplemented by wives and non-members, some felt that the supplementary things, such as the Convocation, added to the interest. Some thought the film not wholly representative of the Annual Session, because it omitted exhibits, clinics and panel discussions, except by brief reference by word of mouth."

DR. FITZ: "If this is done right, a scenario would have to be prepared of the entire picture."

DR. PINCOFFS: "We will now proceed to the report of the Committee on Finance, Dr. A. B. Brower, Chairman."

DR. A. B. BROWER: "The Committee on Finance met at the College Headquarters on November 17, 1951, with Doctors A. B. Brower, Chairman, Walter B. Martin, Walter L. Palmer, the Treasurer and the Executive Secretary in attendance. Messrs.

Lee and Beardsley, representatives of the Investment Counselors of the College, Drexel & Co., met with the Committee to discuss the College investment policies and the present portfolio.

"Among communications was a letter from Dr. Lyle Motley, F.A.C.P., of Memphis, Tenn., suggesting the possibility of lowering the fees and dues of Mexican members, due to the low rate of exchange between Mexico and the United States. It was the unanimous opinion of the Committee that there is no manner available by which such an adjustment may be made in our present policy."

. . . On motion by Dr. Wallace M. Yater, duly seconded, put and carried, the recommendation of the Committee with regard to the dues of Mexican members was approved. . . .

DR. BROWER (continuing): "At the previous meeting of the Committee, the Treasurer and the Chairman of the Committee were directed to secure three separate analyses of the present security holdings of the College, with regard to diversification of security holdings; that is, with respect to bonds, preferred stocks and common stocks. These reports were carefully studied, and it was found that each investment specialist varied considerably in his opinion of the diversification of securities, and after discussion with Messrs. Lee and Beardsley, the Committee only considered it desirable to reduce our total investments in common stocks by approximately 10%, the proceeds to be invested in bonds, after obtaining specific recommendations from Drexel & Co.

"The Committee reviewed all security transactions that have taken place since the last meeting of the Board of Regents. Submitted for record and approval by the Board of Regents are the following Endowment Fund transactions. (Dr. Brower listed the details of security transactions affecting the Endowment Fund, and a motion was adopted approving the action of the Committee on Finance. He also listed sales and purchases of securities recommended by the College Investment Counselor.)

DR. BROWER (continuing): "The Executive Secretary will present to you at this time the Operating Statements of the College for 1951, showing on pages 1 to 3 the actual experience from January 1 to September 30, 1951, and on pages 4 and 5 the estimated expenditures and receipts for October, November and December, 1951, disclosing an estimated surplus in the General Fund Account at the end of 1951, $74,-965.92. This compares with a year ago to $72,609.57.

"On pages 6, 7 and 8 are shown the Operating Statements and Budget Comparisons of the various departmental budgets in full detail, and on page 9 there appears a summary of all budget expenditures, compared with budget appropriations, disclosing that the College will have operated during 1951 within its budget, with a remaining estimated surplus of $4,362.24.

"For the information of the Regents there appears on page 10 a comparative operating statement on the 'Annals of Internal Medicine' for the past three years; and on page 11 a comparative operating statement for the Annual Sessions for the past three years.

"*1952 Budgets:* On pages 13 through 19, the Executive Secretary has shown the detailed budget operations of the different departments for 1951, and has indicated the estimated budget needs for 1952. These are all summarized on page 12.

"The Finance Committee has gone over these in detail and recommends their approval with the following alterations:

> The Committee recommends an addition of $1,000.00 for Traveling Expenses on the budget of the General Chairman of the 33rd Annual Session, this sum being required to cover the traveling expenses of Panel non-member participants;
>
> The addition of $800.00 to the budget for the College Headquarters, to cover the pointing of the architectural tile work of the building, which is believed to be deirable to attend to at once;

The reduction in the budget of the general office of the Executive Secretary by $6,500.00, because the Committee on Fellowships has recommended only four Research Fellows instead of six;

The addition of approximately $3,000.00, or 8%, on the salary appropriations for the staff members of the Executive Secretary's Office as adjustments in living costs, the salary increases to be made at the discretion of the Executive Secretary from the standpoint of merit.

With these alterations, the estimated income for 1952 will be $335,090.00, and the estimated expenditures, $285,261.71, leaving an anticipated surplus in 1952 of $49,828.29.

"On behalf of the Committee, I move the approval of this report and these recommendations."

. . . The motion was seconded by Dr. Cyrus C. Sturgis, put and carried. . . .

PRESIDENT PINCOFFS: "I shall report in a summary way on the meeting of the Consulting Committee on Annual Sessions. This Committee has met to consider with Dr. Roy W. Scott, Mr. E. R. Loveland and myself the progress made in providing for the Annual Session in Cleveland. I shall first speak concerning that portion that falls to the lot of the President. First, I propose to change the title 'Morning Lectures' to 'Morning Symposia.' These will be held twice during the week, on Wednesday and Friday mornings. I have organized four Symposia, so there will be two each morning. Each will start with a lecture on the basic pathological physiology of the subject, to be followed up by short topical papers meant to bring the hearers in touch with the recent developments in the field under discussion. Arterial Hypertension, Thyroid Diseases, Rheumatic Fever and Diabetes are the subjects of the Symposia.

"I owe a great debt of appreciation to numerous advisers on the selection of papers, both for the Symposia and the Afternoon General Sessions. In general, I have been guided by the digest of the criticisms made of former Annual Sessions, which I think are not so much criticisms of what was done as an expression of the feeling on the part of our increasing number of young members as to what they would like to see at the meetings, or the moving of subjects a little closer to the frontier of medicine, and not substitute so many surveys of the field as specific pieces of advanced work. Therefore, there will be quite a number of young men presenting their own work in the afternoons.

"On the Convocation it falls to the lot of the President to select the orator, and I have asked and received the acceptance of Dr. Raymond B. Allen, F.A.C.P., President of the University of Washington, who has had a career in medicine and medical education prior to his being made President of that University, and who I feel will give us a very interesting discussion, probably on some problems of the day in medical education.

"Dr. Scott, the General Chairman, has authorized me to report for him briefly on the status of the program for which he is responsible. He is already advanced very far in completing his program of Panels. There will be four Panels a day on four days of the meeting—Tuesday through Friday. He really has a galaxy of talent in the names of those on the different panels. In addition, on each of these days he will introduce a new feature, a Clinical-Pathological Conference, conducted at the same time as the Panels. He has obtained a great many well known names, both in pathology and medicine, to conduct these C-P Conferences. He and I are both very interested to see with what reception they meet.

"There was also a meeting yesterday of the Television Clinic Committee, the representatives of Smith, Kline & French, as well as the Chairman of the Committee, Dr. John D. Battle, Jr., who is doing a splendid job in making tentative arrangements

for the Clinics, chiefly in two hospitals, which will be televised from the Cleveland Clinic to the Auditorium. There will be from sixteen to twenty television units at the Auditorium, calculated to accommodate an audience up to nine hundred. These TV Clinics will run every morning for four mornings and in a measure will be in competition with the Symposia.

"By common agreement, we have decided to start the morning programs at 9:00 a.m., and we are going to break them at 11:00 a.m., with a period of forty-five minutes, then start the Panels at 11:45 a.m., and give a good full hour to the luncheon period before the 2:00 p.m. afternoon sessions. It is hoped that starting a little earlier, with a somewhat longer pause in the afternoon, will also please our exhibitors.

"The entertainment on Monday evening has been arranged for by Dr. Scott. It will be a musical type of entertainment with the internationally known Orpheus Club performing in the Music Hall. There will also be a widely known violinist who will contribute. I am told that the arrangements for the entertainment of the ladies are going to be quite extensive, and they are already well under way. I will ask Mr. Loveland to report briefly on the administrative features."

MR. LOVELAND: "While all the first-class hotels will be utilized to accommodate members and guests attending this Session, the Hotel Statler has been designated as headquarters for the Officers, Regents, Governors and Speakers on the Program. Reservations for this group, as usual, will be handled through the Executive Offices, whereas reservations for the members and guests-at-large will be handled through a housing bureau conducted by the Cleveland Convention Bureau. Special reservation forms are being printed and will be distributed to all members.

"Physical arrangements for the meeting are not wholly ideal, because the exhibits and certain of the panel discussions and the television programs must be conducted in the sub-basement, whereas the halls for the General Sessions and Morning Symposia are located on the floor above. A new feature this year is an extensive electron cardioscopic exhibit by Dr. J. Scott Butterworth, F.A.C.P., of New York City. The rooms to be used, though not on the same floor, are generally excellent. Their capacities are good. We shall have an exceptionally fine Technical Exhibit, the income from which should be over $30,000.00."

PRESIDENT PINCOFFS: "Perhaps I have rushed this meeting along a little fast, but that was so we might have time to consider a report of fundamental importance to the future of the College.

"If I may lay a brief background for this before calling upon Dr. LeRoy H. Sloan to report, I should like to say that there has been for a great many years concern in our minds and in those of the Governors as to the future size of the College, as to the composition of its membership and as to the nature of the criteria which should determine admission. This led to the formation of a special Committee at Boston under the Chairmanship of Dr. Charles A. Doan, who devoted a great deal of time and thought in drawing up a report to the Governors, presented at the St. Louis Session.

"The essentials of this report were that once an Associate was elected, he would remain an Associate in the College for life, unless he were elevated to Fellowship. This was recommended by the Committee partly on the basis that it would be possible at any time for particularly distinguished service to make a man a Fellow, giving more the chance to elevate the standards for Fellowship over the years, because there would be no such pressure as presently exists when a man must attain Fellowship in five years or be dropped; partly because the Committee foresaw a danger that with the dropping of considerable numbers of men each year there might arise a spirit of discontent which might lead to the formation of some rival organization. The Governors approved the recommendations of the Doan Committee with only one vote

in opposition, and they have submitted these recommendations to the Regents. The Regents authorized the President to appoint a Committee to study these recommendations and bring before this meeting the recommendations it felt desirable for action. Dr. Sloan was named Chairman of that Committee, and he will mention the names of the other members in his report."

DR. SLOAN (showing slides): "Meetings of the Board of Governors or its Committee were held April 8, 11 and 13, 1951, and their final recommendations then were:

(1) Certification by the American Board of Internal Medicine, or an allied board, shall be a prerequisite for election to Associateship;
(2) There shall be no limit to the term of Associateship;
(3) Associates shall (a) have been Associates at least for three years, and (b) shall show evidence of progressive professional attainment and advancement before consideration for election to Fellowship.

"The special Committee appointed by President Pincoffs met at the College Headquarters on June 11, 1951, attended by Doctors Maurice C. Pincoffs, Roy R. Snowden, T. Grier Miller, Walter L. Palmer, J. Owsley Manier and LeRoy H. Sloan, Chairman. They discussed the Doan Report at great length, and one of the suggestions made was that we must consider the qualifications for Associateship and for Fellowship as other things than the ones we have been talking about, namely, character of the individual; what motivated him to study medicine; his emotional stability; his mental equipment and training. Part of these was to be determined by the publications which he might produce, by the impressions which he had made in the community and by the impression he had made on the regional committee, and by an individual interview with the man; also, in the case of Associates, by his attendance at the College meetings, whether he has attended any meetings after becoming an Associate, his reaction to a questionnaire to be sent out by the Central Office concerning the obligations of an internist. These suggestions in the special Committee came largely through Dr. Miller. In addition to that, the Committee took up the matter of addressing a directive to all Governors, that directive in a general way to suggest to the Governors that they follow up Associates in their territories, that within a year or so they review their list, consider what men are making progress, which are not, etc.

"The Committee also felt that we must clarify the atmosphere a little bit on the requirements necessary for Direct Fellowship. One suggestion was that there be both 'Members' and Fellows, the latter constituting more of an honorary group who would be selected, distinguished gentlemen. In other words, a plan that would approach the pattern of the Royal College of Physicians of England.

"Another suggestion was that there should be proposed by local Fellows in the community only outstanding internists and physicians for Direct Fellowship, and that Associates be done away with altogether. In other words, if you had a man in your community who was an extraordinarily well prepared and distinguished internist, you might recommend him for Direct Fellowship without his being qualified in some other manner.

"Then that introduced the idea of Membership and Fellowship—questions of voting power, who would run the College. Would the 'Members' run the organization, or would the Fellows, with the Regents and Officers, run the organization? That was largely based on an appreciation of the fact that the American Board of Internal Medicine now certifies approximately 700 candidates a year.

"Then there was a suggestion that the Associate term be altered and be changed from five to ten years. At that meeting these motions were made and carried:

(1) Governors shall appoint a committee of three to five members, with staggered terms; each member not to serve more than five consecutive years;
(2) Certification by the American Board of Internal Medicine, or other appropriate board, should be a prerequisite for election to Associateship, except under very exceptional conditions;
(3) The term of Associate membership shall be a minimum of five years and a maximum of eight years;
(4) A statistical study shall be made by an actuarial expert as to the potential number of Fellows and Associates in the future.

"A motion was lost that there shall be no limit to the term of Associateship—in other words, the idea that we have a permanent Associateship was lost.

"The Committee met again on November 16, 1951, at the College Headquarters, with Doctors Charles A. Doan, T. Grier Miller, J. Owsley Manier, Maurice C. Pincoffs and LeRoy H. Sloan, Chairman, in attendance.

"There was a general discussion of the recommendations from the meeting held in June and of communications received from various men, Doctors Blankenhorn, Miller, Pincoffs, Doan, and others.

"I may say that the Board of Governors may feel quite proud of Dr. Doan, who really presented his ideas, and those of the Board of Governors, in a very impressive fashion. Dr. Doan believed that there should be a membership certified by the American Board of Internal Medicine, representing internists of the country, without age limit, with no total membership limit and with a flexibility which would parallel the changing national pattern. The interpretation of this we will leave up to you. He believed that there should be a three-year probationary period, during which time an Associate must continue his contributions to clinical and research medicine, in order that he may show he is worthy of Fellowship. His election to Fellowship would be recommended by the Fellows of the College in his community. He would not be picked out from the group by the Board of Regents or by the President, or any one of that sort, but would be nominated by the local Fellows. There would be no limitation to the increment of Fellows in the College—the number could rise to any size. For Direct Fellowship it would not be necessary that the man shall have been certified by his specialty board, but that any individual who you thought adequately qualified could be recommended for Direct Fellowship.

"As far as Masters were concerned, Dr. Doan's idea was that any Fellow was eligible at any time, and that Mastership would simply honor exceptional service.

"Officers would be elected from Fellows and Masters only by nomination by the Board of Governors and the Board of Regents; a full vote of the Associates, Fellows and Masters for all Elective Offices. In other words, under his plan the control of the College would go completely over to the final vote of Associate members at large.

"Another suggestion discussed also was to give up Associateship completely, and have only Fellows in the College. This would mean that the Credentials Committee would have but one investigation of a candidate, and when a man was made a Fellow he would be such all his life, unless he grossly transgressed the ethical concepts of the College. It was felt by several that the prestige of the College would go up and certification would be much less important. This we think is well worth considering. The other suggestion was again that we have two classes: 'Members' forever, and Fellows selected by the Board of Regents.

"The following proposed reorganization has been contributed: Associates having full voting privilege on any and all matters originating at this level; largely practicing internists; represented by the Board of Governors, channeled through the Board of Regents. Fellows and Masters; recognizing continuing contributions; represented by the Board of Regents and channeled through the Regents.

"The Committee suggested that we have an actuarial study made, and this has been completed under date of November 8, 1951.

"Of the present 5,226 Fellows and Masters,

4,739 will be living in 1955;
3,350 will be living in 1965;
1,916 will be living in 1975.

"We have 78 Associates at present who are sixty or over, and who, because they attained Associateship automatically through the old American Congress on Internal Medicine, are under no obligation to qualify for Fellowship. Of these, 60 will be living in 1955, 22 in 1965, 4 in 1975.

"We have one member presently one hundred and two years of age; we should honor him!

"Now, the membership of the College totals in all, 7,071. Of the Associates that have been advanced to Fellowship you will notice that the number has been gradually increasing:

Associates advanced to Fellowship:

1947	186
1948	213
1949	270
1950	313

Associates dropped:

1947	42
1948	66
1949	89
1950	182

"In spite of the resignations we are advancing, according to these statistics, more men each year. The worst year, 1950, which represents the accumulation of a great host of Associates elected prior to or during the War, and whose terms were extended because of military service, represented the discontinuance of 182 Associates, but in spite of that, the College elevated a larger number of men to Fellowship.

"What would be the increase in membership if we follow the present general trend—if we keep the College as it is and take as a base age for Fellowship forty-two years, and if we advanced 300 members annually—there would be the following increments to membership:

1955	1,189
1960	2,622
1965	3,974
1975	6,298

"The total Fellowship then would be as follows:

1955	5,928
1960	6,690
1965	7,327

"Add to these figures the 2,000 approximate Associates, and you will have the total membership. About 1966 or 1967, we would have about 10,000 members in all.

"In order to incorporate further data, we had to consider what the American Board of Internal Medicine is doing. These are their present figures:

Total certified without examination	1,945
Total certified by examination	5,170
Grand Total	7,115

Per Cent of Failure:

Written examination:

1938	1.2
1939	19.
1942	37.
1945	31.
1947	41.
1950	51.

Oral Examination Failures:

1938	14.
1939	25.
1942	27.
1945	8.6 to 26.
1947	12. to 26.
1950	26. to 43.

"In 1948, 1,043 took the orals, and 624 passed; in 1949, 1,182 took the orals, and 760 passed; in 1950, 1,564 took the orals, and 760 passed."

DR. PALMER: "Those figures aren't quite correct. They may be correct in regard to the number that passed, but they represent carry-overs from previous years, re-examinations, etc. The percentage is not right, but the total number certified in those years is correct."

DR. SLOAN (continuing): "With the knowledge that it had, the Committee on November 16, 1951, rescinded the motion that certification should be a necessary prerequisite for Associateship. Part of that was due to the feeling that there is a group of individuals which should be taken in where certification might not be too important or even possible. The Committee suggested the term of Associateship shall be a minimum of three years and a maximum of ten years. Dr. Doan thought the Board of Governors would probably accept this minor compromise.

"The Committee confirmed that the Governors should appoint a committee of three to five members, with staggered terms, to function with the Governor in relation to proposals for membership; the terms of each committeeman should be limited so that the same man shall not serve more than five years consecutively.

"Also, it was suggested that before any really serious alteration in the framework of this College be made that we study the framework of the Royal College of Physicians; that we determine the voting power and authority of its members as distinguished from its Fellows; that we learn the technic of the Officers, methods of election, etc.; that we determine the percentage of Fellows, the percentage of Members; financial requirements of Members and Fellows, and that we develop newer and broader requirements for both our Associates and Fellows. We then are left with this:

(1) We have recommended on the second vote of our Committee that certification shall not be a prerequisite for Associateship;
(2) We have recommended on an affirmative vote that the Governors shall have the directives mentioned;
(3) We have changed the term of Associateship from a maximum of five years to a maximum of ten years,

and we have suggested that before any radical change be made in our framework, a further study shall be pursued.

PRESIDENT PINCOFFS: It might interest you to know that on the basis of the analysis made by actuarial methods of the life expectancy of the present Fellows that we could take 200 new Fellows in a year for twenty-five years and only increase the number in the College by less than one thousand. I think that this actuarial study very well justifies itself. It gives us an idea of the attrition rate in the College and what its increase in size would be at varying rates of election of new Fellows. Before opening this matter for discussion, I should like to point out that, whereas Dr. Sloan so graphically showed, this Committee had a number of ideas before it came to a conclusion, it did come to a definite conclusion and definite recommendations. I think it was influenced by two main considerations; first, that while final authority rests with the Regents, we must take into consideration a practically unanimous vote of our Board of Governors if any change is made in our present system. There has appeared to be a certain dissatisfaction with the status quo; second, a good deal of weight in leading this Committee to this final recommendation was the feeling that a rigid five-year period for Associateship, coming in the prime of the internist's life when he carries some of the heaviest burdens of small income and young family and a great deal of work in his hospital and medical school, with the additional responsibility of passing his boards and showing some distinguished accomplishments that would entitle him to Fellowship, is not entirely a fair requirement—that we are probably letting men out from Associateship and out of the College without really giving them long enough to prove what they possess. It was on that basis, I think, that it was thought that to give an increased term of Associateship would be a fairer procedure. For those that believe we will eventually come to a permanent membership, plus Fellows, this plan will give some trial and error during the coming years as to how it would affect the incentive of the Associate to prove himself. The reason certification as a prerequisite for Associateship was rescinded after further discussion, in my opinion, was that it was felt that one of the most valuable things the College does is to help the young man, through affiliation with us and through the advantages he gains thereby in our meetings, both national and regional, and through appearing on some of the programs, and his priority in attending our various courses at a lower fiscal rate. In all those ways the College offers a great deal of help to the young man to pass his boards. It was felt also, at least by some of us, that if the College offered him little during all those years and he passed his boards, we would have missed the opportunity of indoctrinating him in the ideals of this College, a home for him during his internist's career—that we had missed the opportunity of doing this for him during his most formative age, and that, therefore, the Committee rescinded its earlier decision to make certification a prerequisite for Associateship. This is a radical move, and it seems to me that it is deserving of a great deal of discussion here and now. This proposal can be totally rejected; it can be sent back to the Committee for further study; it can be approved, and, if approved, it can be referred with the approval of the Regents to the Board of Governors. In other words, it could be approved in a contingent form that both the Governors and the College should approve these changes before they become law. In that case, perhaps, the method of procedure might be an approval, carrying with it the spirit of these recommendations, or as amended, by the Regents and referred to our Committee on Constitution and By-Laws to be put into the form of an amendment to the By-Laws and then presented to the Governors at their meeting in Cleveland, and, if approved by them, presented at the Annual Business Meeting to the general membership. Certainly wide approval should precede any such radical change. I merely offer these remarks, and to some extent personal opinion, as a prelude to our discussion."

DR. T. GRIER MILLER: "Mr. President, I am going to make a motion that we approve the recommendation of the Committee, but I do want to say, in that connection, that I personally voted for this action on the part of the Committee with a great deal of reluctance. I personally do not approve of this extension of Associateship for ten years, but I do think if we take this action we shall temporarily satisfy the Board of Governors, and it will give us a chance in the next year or two to work out a solution that will be satisfactory to all of us."

. . . Dr. T. Grier Miller made such a motion, which was seconded by Dr. Alex. M. Burgess and opened for discussion. . . .

DR. BURGESS: "Having followed the steps very carefully, I feel that the solution reached by the Committee is a very definite step forward. I am particularly pleased by the absence of emphasis on certification by the Board. I have come to believe, after having worked five years on the Board, that with all its virtue and the good that it has done, I still think it is a weak reed on which to lean so heavily, and I feel very badly about the fact that the Services, particularly of the Veterans Administration, lean as they do upon it. I think it is bad that the College should lean so heavily upon it.

"I am impressed by the fact that every member of the Board is an internist, is a man doing his utmost to make the Board work, and I thoroughly believe that the examinations are the best of any Board that exists. In spite of that fact, I believe there is a large error in their final conclusions on individual candidates, at least 20 per cent, and that is based on the fact that it is utterly impossible to examine such a large group of men in the limited time allotted and get anything like an accurate estimate of these men. Therefore, I believe that a method as suggested by the Committee, by which the results of the examinations of the Board can be by-passed in appropriate cases, is a very important thing and that there are many people who are unable to pass the Board examinations who certainly should be Fellows of the College."

DR. FITZ: "I rise to a point of information. I understand that the motion has been made that we accept the report, but in so doing, do we agree to adopt the recommendations contained therein? If we do that, I would understand that that would require a change in the By-Laws and possibly in the Constitution."

PRESIDENT PINCOFFS: "If we accepted the recommendations, I would like to see a later motion made that that acceptance be contingent on an acceptance likewise by the Governors, prior to any action to pass upon an amendment to the By-Laws which would embody these recommendations. In other words, what I would like to see done is that if this body today approves these recommendations, this Board instruct me as President to turn these recommendations over to the Committee on Constitution and By-Laws to be drawn up in proper form to become incorporated, and that we then transmit to the Governors, preferably ahead of time of the next meeting, this action by the Board of Regents and this suggested amendment to the By-Laws, and do not proceed with the matter until they have either stated that they do not wish to accept this proposal of the Regents, or until they have accepted it. It is true the actual power resides in the Regents and we do not have to have concurrence of the Governors, but in my opinion it would be certainly unwise, when the Governors have recommended one thing and the Regents have radically altered it, for us to go ahead to put it into the law of the College without first resubmitting it to the Governors. The College should do this as a whole, rather than the Regents making the decision. The matter affects the Governors very directly, and they have made a very specific recommendation."

DR. FITZ: "May I ask Dr. Sloan to restate exactly what the original recommendations of the Governors were, and exactly what the Committee has finally recommended?"

DR. SLOAN: "There were originally three recommendations from the Doan Report:

(1) Certification as a prerequisite for Associateship;
(2) No limit to the term of Associates;
(3) The minimal Associate term shall be three years.

"The present Committee recommends against certification as a prerequisite for Associateship; it recommends that the minimal Associate term shall be three years and the maximal, ten years—not unlimited. The present Committee added the recommendation that a Governors' Committee be appointed to assist the Governors—a secret committee appointed by the Governor himself—through which all proposals for membership will be filtered. If this Governor's Committee shall recommend a candidate highly, the proposal will be endorsed by the Committee and transmitted to the Committee on Credentials. We also envisioned that we should have to draw up a little more specific requirements for Direct Fellowship, and we thought it would be desirable to study the framework of the Royal College of Physicians of England, to see how they handle these matters."

DR. PALMER: "As I see it, the essence of the Doan Report has to do with two points: (1) the requirement of certification as a prerequisite for Associateship, and (2) the abandonment of any time limit on the Associate term. As to the second point, I think the Governors have a good point. Excellent men have been dropped from Associateship in the College because they had not published or contributed adequately. That is setting up in the long run a category of excellent internists over the country who do not qualify for and cannot be members of the American College of Physicians because they haven't contributed, and that is likely to wind up in the establishment of a competing society, an International College of Physicians. Of course, one of the reasons these men are dropped is because the Credentials Committee is anxious to maintain standards and get the American College of Physicians on an ever higher and higher plane, and because we are anxious to keep the total membership of the College down. I am not sure that either one of those goals is desirable. I think this organization ought to have a broad base and that it should include the competent internists of the country, regardless of whether they have published or not, and, furthermore, I think that we shouldn't be too obsessed with the matter of size of the College. It is up to us to find some way to run annual meetings, to take care of these men who come in, if they are competent internists.

"Coming back to Dr. Pincoffs' point, one reason for doing away with the requirement of Board certification is that we want these young men as Associates in the College so that they can be nurtured by the College and enabled to pass the Board examinations. If we are going to do that, we are going to take in a large number of men—a large group of Associates, much larger than we now have. If we are going to do that job effectively, we have got to cease worrying about size.

"In regard to Board certification, I agree completely with the point of view taken by Dr. Burgess. In my initial period of service as a Governor of the College, I, likewise, agreed completely with that point of view, but before I terminated my experience as Governor, I changed my mind and was persuaded that certification is very helpful to the Governor, and that it does serve a useful end. I am, therefore, inclined rather to the view of the Doan Committee and the Board of Governors. The idea of requiring certification as a prerequisite for Associateship originally came from the Credentials Committee to the Board of Governors, and, as you will recall, it was repeatedly rejected by the Governors until finally when incorporated in the Doan Report it was passed practically unanimously, and, I may add, to my amazement. I finally came to the conclusion that that was the best plan, provided provision is

made for the election of occasional otherwise well qualified individuals as Associates or as Fellows in the College.

"I am prejudiced in favor of the Doan Report. I am also inclined to wonder, however, if Dr. Miller's suggestion of the abandonment of Associateship may not be the best plan or solution. When a man has passed his Board of Internal Medicine, or the equivalent, or, under exceptional circumstances, does not have to, then take him directly into Fellowship and be done with it and no longer worry too much whether that number be five thousand or ten thousand."

Dr. Charles F. Moffatt: "Perhaps you might be interested in my point of view as a relative outsider. I am very glad to hear that they propose to analyze the procedure of the Royal College of Physicians of England, because with England the membership, which is entrance by examination, is very highly desirable and very much thought of. The Fellowship is more, an honorary degree. Now I am looking at this from an outside point of view. Perhaps you gentlemen are too near the picture, but I am sure you realize that this country has become and will ultimately remain the mecca of medical science, the mecca of research in clinical medicine. The only way that outsiders can recognize such a thing is either through the publication of certain articles or the intimate acquaintance through Postgraduate Courses, so that you have no distinctive degree which determines your top men. What does Fellowship in the American College of Physicians mean? There are hundreds who have gone through the Board of Internal Medicine; some have gone through the Board of Public Health, or the Board of Pediatrics, and yet they may all be Fellows of the College. To an outsider, Fellowship is not of any great distinction as it should be, so I think great emphasis should be put on the promotion from Associateship, or membership, up into Fellowship."

Dr. Yater: "Mr. President, I don't think the present recommendation is going to be sufficient for the Governors. I have been on the Credentials Committee a long time, and I have come to feel that their method is the proper one, and Dr. Moffatt, I think, backs their recommendations. The only additional thing I would suggest is that we limit the College membership entirely to internists. Now we take in many members from allied specialties. Those men have their own particular organizations. Why not limit ours to internists?"

Dr. Howard P. Lewis: "On my part, I am in favor of the Doan Report as submitted, except I would like to see the name of Associate dropped and the name of 'Member' substituted. Speaking from the standpoint of my community in the West, as regards the American Board certification as a qualification for membership, I can think of only one instance where a man who I would think qualified to belong to this society was unable to attain certification by repeated trial. I doubt very much if certification is too much of a hurdle to ask of a candidate as one of the qualifications for this society. At the same time, I know that in my community it is exceedingly difficult for a first-rate internist to qualify for Fellowship in the College under the present rules. Many of these individuals are highly qualified practitioners of internal medicine and do an extraordinarily creditable job of taking care of patients in that field, but it is practically impossible for them to turn out a worth while piece of clinical investigation. It is difficult for them to compile an adequate and competent written speech that might be acceptable. There is a smaller group of men who have a primary interest in investigation who are willing and able to cut down some of their private work to be able to pursue such an avenue of work. These can turn out creditable pieces of work and do so. It would serve our purpose very well if we had what we might call a 'Membership' in the College which would have all the rights and privileges that go along with Fellowship at the present time, with certain exceptions perhaps, which would be a life-time affair, in which a man who could pass the initial qualifications could remain for the rest of his career and enjoy all the ad-

vantages offered by the College. I think we would have to impose some entrance requirements for that 'Membership' that would be adequate to assure us that this is indeed a man whom we want to take and who we feel sure will be an individual who could profitably remain with us for the remainder of his clinical life. I should think it would not be too much to ask him to attain certification and present other qualifications that we might set up.

"I would then like to see the Fellowship reserved for those physicians who either in teaching or research, or by distinguished service and eminence in medicine, are granted Fellowship as a mark of distinction. Fellowship could carry with it a real mark of attainment, and at the same time it would be a real spur to those men that I think should become Fellows, because they will start working for that, and they would be totally dissatisfied to sit in the position of a Member indefinitely. There would be two parties given equal opportunity:

(1) A group that is busy in practice, to stay with the College and practice;
(2) The group that would like to excel and carry on further."

DR. MILLER: "Mr. President, I am very much interested in what Dr. Lewis has said, but if we do that, we are simply creating two classes of membership in the College, one of which will be just the same as the Association of American Physicians. That is a very highly select small group made up of teachers, productive workers and researchers, and I don't see any point in it. Furthermore, we should have a great deal of discontent and dissatisfaction, perhaps even more than at present, among those who are simply 'Members.'"

DR. J. OWSLEY MANIER: "I think the thing that is pertinent in this discussion is the place of the American Board of Internal Medicine. At present a man who becomes an Associate has to pass the Board before he can qualify for Fellowship. I believe the vast majority of rejections that have come in advancing Associates to Fellows arose from the fact that men either did not or could not pass the Board examination. Now, if you adopt the Doan Report, which was a beautifully written affair, and, as I see it, brought about by two motives (1) that all qualified internists be in one great organization, and (2) the element of fear that, under the rate of rejections, a competing organization would develop— getting away from the emotional problem, you still have the same problem with the men who do not or cannot pass the Board examinations. That is fundamental in his report.

"I would agree very much with Dr. Lewis, and always did, and I have sat on this Credentials Committee and agreed that there should be other qualifications than the number of publications that an individual might produce. Dr. Pincoffs stated to this body some ideas that were fine, that men should be credited not only for publications, but for teaching, research, community service and participation in hospital, intern and postgraduate programs. Personally, I could never get away from the idea that if you were to create a permanent group of such people that you would still have a great number of people who will never have the incentive to progress. On the other hand, if you accept the recommendations of the present Committee and in some manner issue a directive to the Governors' Committees to consider other things than publications and contributions in determining who might be qualified to come into this organization, the trouble that we have had could be averted."

DR. PALMER: "May I ask Dr. Manier what he would do with a young man who is certified by the Board and is endorsed by the Governor as an outstanding practitioner in the community, but has contributed and published nothing? Would you take him in as a Fellow?"

DR. MANIER: "Out of these Governors' Committees that have been suggested would undoubtedly come the adequate information that the Credentials Committee needs to act fairly and properly. If you adopted Dr. Doan's report as it stands, I

think he has in mind that a man who graduates in medicine, takes his full five years of postgraduate training, has two years in practice, passes the American Board and is morally and ethically satisfactory, would be taken almost automatically into the College. I would say that a good many men now pass the Board after only two years, and if you can tell me anything of how you are going to find out how morally and ethically satisfactory he is in just two years and what he is going to do in the future, I would appreciate it."

PRESIDENT PINCOFFS: "We have been asking Associates in five years to pass the Boards and to show something more of their progress, or we have thrown them out. Now it is proposed we do exactly the opposite, that we get them to pass the Boards and then take them in for life shortly thereafter. I am very dubious about that. I am dubious on the administrative side also. A rough estimate was made in the Committee which had two assumptions; first, that we take in Associates after passing their Boards, paying some attention to the figures of those that pass the Boards and our present rate of admission of Associates, and, second, that instead of making Fellows out of approximately 75% of our Associates, we so raise the Fellowship standards that we would only make Fellows out of 25% of the Associates, and the rest would remain status quo. On that basis, after a term of years, we would have a College composed of about 3,500 Fellows and about 7,500 permanent Associates. Who is going to run the College? If we have, as we now have, an open meeting, are we going to say the open meeting is for Fellows only, and they will have to show cards at the door to be able to come in and vote? What are the 7,500 permanent 'Members' going to think of that? On the other hand, if we have 7,500 men who are eager to become Fellows, and many of them will be resentful because others have been chosen to be Fellows and they have not, will we not have within the College a considerable disgruntled group, who might very readily, if they have a vote, take possession of the College? In a very brief period of years every Governor would be selected by the Associates, as would also the Officers of the College. I don't want to paint a dark picture or to malign possible Associates, but I think that is a very practical question in considering the Doan Report."

DR. PALMER: "A pretty high percentage of the Associates now coming in have already passed their Boards, but if we lower the requirements and take them in to be nurtured so they can pass the Boards, and we let them stay in ten years, then what are we going to do at the end? Are we going to take them or drop them?"

PRESIDENT PINCOFFS: "I wasn't aware that it had been proposed to lower the standards for Associateship—maintenance of the status quo on the Associates or considerably raising the standards."

DR. PALMER: "You cannot raise them much without making certification a part thereof, because my understanding is that well over half of the candidates for Associateship are already certified, and that probably up to 70% of those elected to Associateship are certified. From this previous discussion, I am afraid that we are really going to lower the entrance requirements. In the Chicago area it is very difficult for some one to get in unless he has already passed his Boards, but my point is this, if we take them in to Associateship and let them stay in for ten years and then drop them for some deficiency, we shall have made enemies, and shall be worse off than if we had never taken them in at all."

DR. YATER: "The only real change that is presently proposed is extending the Associate term to a maximum of ten years. The present method of electing Associates remains. They must have the basic requirements for admission to the Boards, and we decide that. Then they must have at least two years' residence in the community and in practicing internal medicine. After election to Associateship, the present recommendations merely give them ten years instead of the present five years to qualify for Fellowship."

PRESIDENT PINCOFFS: "The emphasis in our discussion was intended not so much to emphasize rescinding the recommendation of certification as a prerequisite for Associateship, but rather to give Associates a longer time in which to show something distinctive that would warrant their elevation to Fellowship. The Committee agreed, though it passed no formal motion, that a method should be devised whereby the record of each Associate from year to year during his ten years be kept in some regular way, that a form be devised on which he would report annually, through his Governor to the College, on his activities—elevations in teaching rank or hospital rank, committee and medical society activities, publications, addresses, etc., a whole series of things falling into different categories of medical activity—that he be assessed after his third year on these records and on what the Governor's Committee and the Governor know about him, and if in ten years that man's record contains nothing other than that he is doing the practice of medicine in a legitimate and proper way, the Committee would not elevate him to Fellowship. Under such conditions, I do not believe he would have too much reason to feel aggrieved. I don't believe he would have nearly the ground for feeling disgruntled that he has now, nor would there be the unfairness that now exists in dropping him at the end of five years."

DR. FITZ: "Which of these two plans do you feel, from your knowledge of the Constitution and By-Laws, is going to be the least upsetting to the concept on which the College has already gone, and is either going to change the character or government of the College, or are we talking about details within our present framework?"

PRESIDENT PINCOFFS: "Dr. Fitz, I would like to have Dr. Sloan answer you also, but I would feel that lengthening the term of Associateship would not change fundamentally the going concern of the College, and that adopting a permanent membership at this time, without any period of trial, would be a very radical step and would fundamentally alter the By-Laws of the College, and, to some extent, the concept of the College as it has existed."

DR. ASA L. LINCOLN: "Mr. President, as a very recent Governor and now as a Regent, it seems to me there would be less discontent among the Associates if we follow the Doan Committee recommendations. If a man is required to be certified before he can be elected an Associate and no limit is put on the Associate term during which he shall qualify for Fellowship, it leaves entirely to the candidate himself the responsibility of qualifying for Fellowship. If he cannot show cause for advancement, it will be by his own fault, and he needn't feel aggrieved. He can remain an Associate and can have the advantages of the College."

DR. SLOAN: "Mr. Chairman, that is going to build up a group which is just what we are talking about. In fifteen years, under that sort of a scheme, the Associates will take over this College, lock, stock and barrel. If you want that, I suppose that is all right, but we feel that the College has been extraordinarily fortunate in the direction of its affairs over these years under the Board of Regents, that the prestige of the College has been maintained on a very high level and should continue to be. If you invite men in and say, 'Boys, you can stick around forever, as long as you pay your dues, and we are going to give you a vote' (that is what the Doan Report says), I think we will soon be top heavy. What the present Committee hopes for is that its recommendations would be passed, in order that not too radical a change in the framework of the College will be made immediately, and that in the next two or three years adequate study can be made of these points and a solution reached. To change the whole base of the College at the present time doesn't seem to me to be wise, and our Committee feels that way also.

"We did not give all of the discussion that developed in our Committee, but we, as Dr. Pincoffs has said, proposed a plan by which the Associate's progress would be accounted for every year, and the records would be gone over not only by the

Governors, but by the Central Office and the Credentials Committee, in order that we might produce a really topnotch Fellow, such as Dr. Moffatt suggested."

PRESIDENT PINCOFFS: "These things have a very definite administrative bearing. May we hear from Mr. Loveland?"

MR. LOVELAND: "I would like to remind you that the Doan Committee was appointed to study ways and means of limiting the membership of the College. The reason was that at the meetings in New York City and Boston, facilities were inadequate to accommodate the members, and there was widespread alarm among the members of the College concerning the organization becoming too large. Actually our Annual Sessions are so well attended that there remain very few cities indeed with adequate accommodations for us.

"The other thing I should like to remind you of are those of history and past experience. Twenty-five or so years ago we had what is essentially permanent membership. There was an affiliate body known as the American Congress on Internal Medicine, and its members corresponded to Associates, whereas the official members of the College were Fellows. The Congress had certain specific powers, including the conduct of the Annual Session. Furthermore, no man could be elected to Fellowship in the College without the prerequisite of membership in the Congress. The Congress had reached that stage where it actually ran the College, because its numbers exceeded several times the number of Fellows in the College. It was Dr. Alfred Stengel (President, 1926–27), Dr. Charles G. Jennings, Dr. William Gerry Morgan, Dr. Charles F. Martin (President, 1928–29), and others, who foresaw that the College was stalled and that it was totally an impractical administrative setup. To change that setup, an agreement was finally executed by which the Congress would be abandoned and its members made automatically and officially Associates of the College, without the requirement of ever qualifying for Fellowship. Straightway a new Constitution and By-Laws were adopted, after many rewritings and amendments, and our present plan of Associateship established. We still have in the College some 78 of those original permanent Associates surviving. A permanent Associateship, as presently discussed, would turn us back twenty-five years and remove, to a large extent, any opportunity to correct mistakes by the Committee on Credentials. The American Board of Internal Medicine today has admitted a 20% error, but it has no chance to correct that error. Not so with the College, under our present plan. The Credentials Committee undoubtedly makes certain errors in the selection of Associates, but they are able to correct, to a large measure, these errors when the Associate comes up for advancement to Fellowship."

DR. GEORGE H. LATHROPE: "Mr. President, the crux of the whole argument so far has been the Associates. Only one or two speakers so far have made any reference to a suggestion which I think ought to be considered, namely, the possibility of giving up the Associate class and having nothing but Fellows. We could readily omit mentioning certification as one of our requirements. That could be left to the Credentials Committee. There are good men in my area who haven't passed the Boards, who won't take them, but, as internists, rank a place as Fellows of the College. Again, the question of publication should be left to the judgment of the Credentials Committee. Through what experience I have had on the Credentials Committee, these publications are often quite important in giving you a definite idea about a candidate. The Credentials Committee does not always stick to a great quantity of writing. It takes into consideration where the man comes from, what his associations are, what hospital facilities he has, and so forth. The Credentials Committee should get more information about the man's character and his standing in the community, not only as a doctor, but as a citizen. If we had no Associates the bars could be slightly lowered for Fellowship, and, perhaps, we would increase the number of Fellows somewhat beyond what we now have and still maintain a high quality."

DR. HAROLD H. JONES: "I am more confused now than I was this morning. In our area we had two men from among the original Associates coming from the American Congress on Internal Medicine. Of these two, I do not believe either one has ever been able to give a paper before a large group of people, but I do personally know that one of them ranks as the top internist of the midwest, and that is covering a lot of territory. He may have certain shortcomings in internal medicine; he cannot talk to a large group of people, other than medical students. He wouldn't receive a recommendation from a Rotary Club or a Chamber of Commerce, but he has the inherent ability and the experience of a top internist. I believe this secret screening by a Governor's Committee might be a step in the right direction, if the Governor would take the opportunity to follow out the plan as Dr. A. B. Brower used to do as Governor, and we would have a far better idea of the candidate's qualifications.

"We have had other men in our community who have been certified and who have become Associates of the College, and at that point ceased to work. As a Governor, I couldn't tell what a new Associate was going to be, whether he would go ahead or just go fishing."

DR. DWIGHT L. WILBUR: "Mr. President, as one of the members of the Doan Committee, I have been very much interested in this discussion. The real problem that is faced in this particular matter is one of a select group in internal medicine, run very ably by the top, that has taken unto itself a large number of individuals who are qualified, much as a reptile often takes a very large meal and hopes that it can digest it. In other words, it is really a College of Physicians that is considering the idea of becoming an American Society of Internal Medicine, because that is actually about what it amounts to, and the question is should we do that. It seems to me that if the College stays as it is now, then it will almost certainly have developed alongside of it an American Society of Internal Medicine, or some similar organization, and, perhaps, that would be the best thing. I am not sure in my own mind at the moment whether it is or not. The College has done a great deal of good. It has elevated the standards in many directions, and it might be wise for it to stay a small select group, run from the top, as it has been, and very ably run. Or, perhaps, it would be best for it to consider the slow transition, which will almost certainly come to it if it takes in the large number of men who are qualified and who will be qualified to meet its standards in the course of the next ten years. Personally, I do not know the answer at present. I think the recommendations of Dr. Sloan's Committee are really a delaying action to give us a chance to make up our minds as to what we want to do, and I think possibly that, or some other similar solution, which will give us a chance in the course of the next year or two to really consider this matter carefully, might at this moment be the best action for us to take."

DR. SLOAN: "Mr. Chairman, there is a motion on the floor by Dr. Miller to approve this report. Would you be willing, Dr. Miller, to take this in place of your motion, that this report be received and that the President be directed to refer it to the Board of Governors for consideration, and such ideas and conclusions and suggestions of that body be referred back to the Board of Regents for further study at the next meeting?"

DR. MILLER: "That is quite agreeable to me."

DR. BURGESS: "I accept it as the seconder."

PRESIDENT PINCOFFS: "There are several who haven't spoken, and there is one I would particularly like to hear from, Dr. A. B. Brower."

DR. BROWER: "I have been very much interested in the discussion, and particularly in Mr. Loveland's report on why the Doan Committee was appointed and what that Committee came up with. The original purpose was to study ways and means of keeping the membership under control, and now the Doan Committee has proposed a plan which, if adopted, would at least double the size of the College. I

think the Committee was a very good one and should be commended, but after hearing all of this discussion, I am convinced there is another side, and possibly we should assume a little of the attitude of the English and have a straight Fellowship College and have that a superior one. If there is another group that wants an international society, let that be a secondary one. We shall still have the one that stands out among them all. I endorse the suggestion of the Committee to study the whole setup of the Royal College of Physicians of England, and that we follow a delaying action here until we are convinced of the right road to follow.

"A great deal of our difficulty in the past arose because the Governors never exerted enough energy in doing the job they were supposed to do, and it is a big job. Now it is suggested that they have four or five committeemen to help them. I think that each Governor should surround himself with as many of the Fellows in his state as he can and present this suggestion to them. If we are going to make changes, it should be done democratically, and shouldn't be done by a few, or by a committee, or by forty or fifty individuals. The voice of the whole Association should be considered, and I think the Governors could do much in finding out the attitude of their constituents. When I return home, I propose to get all the Fellows within my area, and to review this matter with them, and I shall let you know in Cleveland what they think about it. If we would all make that effort, we would contribute something really worth while."

DR. KERN: "Mr. President and Gentlemen, I shouldn't stick my neck out, because I certainly am the Johnny-come-lately in this situation, having had no previous contact with it from any angle until now. What I say is purely that view of the innocent bystander. The thing that started this whole discussion some time ago was the size of the College. Size is something that we will face sooner or later anyway, when it comes to meeting here, there, or somewhere else in the country. It will come sooner if we broaden the base; it will be delayed, but not prevented, even though we have a narrow base. What the final solution would be, I cannot foresee, but that it must be solved some time is inevitable.

"Leaving that point unanswered, I next turn to the second point at issue, and this is most important, whether there shall be permanent tenure of membership, or whether there shall be a class of limited membership. If you are going to have permanent tenure, then, obviously, that permanent membership is going to take over the direction of the running of the College eventually and pretty soon. Therefore, if you are going to have permanent tenure, you ought to have a mighty high hurdle to get in, and that hurdle must include, as I see it, certification. I do not see how you can dodge that issue.

"If you have a limited tenure, then whether you have that limit short or long doesn't get away from the major objection of such limited tenure, namely, dissatisfaction. I don't settle that point. I go on to the next point, which is dissatisfaction itself; and let us not think that there will be no dissatisfaction in one plan and satisfaction with another. We now have limited tenure of membership, and with that we have dissatisfaction.

"But let me cite you the experience of a much smaller group—a microcosm of what happens in our group—what happened to the Allergists. We insisted on permanent tenure and a high hurdle in the American Academy of Allergy; the disgruntled men founded their American College of Allergy; you can't stop them, whether they be disgruntled inside the body or outside the body. From the standpoint of the body itself, it is better to have the disgruntled ones outside.

"Then, if there be permanent membership, there is the question of naming that membership—Member, Associate, Fellow and Master. Now, if you drop the term Associate and substitute the term 'Member' and restrict the term, Fellow, to this upper crust of honored individuals of the future, then what are you going to do with

the five thousand odd gentlemen who at the moment are Fellows of the College? Will they remain status quo until they die, or are you going to ask them to send in all of those follow-up credentials, and if they do not preserve their position are you going to cross off 'Fellow' and make them 'Members.' On the other hand, if you call them all Fellows right from the start, then you will in the high hurdle have practically the same situation that the Royal College has in having a large base of high standard people. It is not too large a base, but still a fair sized one, even as they have elected on top of the membership in England a higher class called Fellow as above Member. Would we expand our Master now to some such superior place? Again a question; not an answer. Finally in the light of these things, I want delay for some time to study this further."

PRESIDENT PINCOFFS: "The question has been called for. The motion is that the report of Dr. Doan's Committee be received, that this report be forwarded to the Board of Governors with a request for their consideration and action, and the matter to be referred back to the Board of Regents for further study at the next meeting in Cleveland."

DR. PALMER: "There is a matter of time involved. I do not know how that will work out. The Governors will not have an opportunity to consider this until Monday or Tuesday of the Annual Meeting."

DR. YATER: "Would it be advisable to send a copy of this report to the Board of Governors soon, so that they will have plenty of time to think it over?"

PRESIDENT PINCOFFS: "I think that that would be very advisable. If the Governors do not have an individual meeting of their own until the middle of the Annual Session, possibly on Wednesday, to formulate their opinion on these recommendations, then they could return the answers to the Regents who will meet again on Friday."

DR. BROWER: "Perhaps it would be well to make it a year instead of trying to close this matter at Cleveland. It would give more time. The Governors could discuss this matter in Cleveland and do some of their homework, and then arrange for decision the next year, which would seem more logical on a matter of such importance."

DR. PALMER: "One objection about that is the personnel of the Board of Governors is constantly changing."

PRESIDENT PINCOFFS: "Such a delay might cause considerable dissatisfaction. Our merely submitting the plan to them offers them a chance to agree or disagree. There is a difference between delay and procrastination."

DR. BURGESS: "Mr. President, if the Board of Governors approve this proposal absolutely it will come back to the Regents on Friday, and if the Regents are not ready to consummate the matter, they can delay at that point. In the meantime, we shall have gone ahead and done something about what the Governors proposed. I think we ought to go ahead with it."

. . . President Pincoffs put the motion to vote, and it was carried unanimously. . . .

PRESIDENT PINCOFFS: "If it meets with the consent of the Regents, I shall forward this action to the Chairman of the Board of Governors promptly, with, perhaps, an informal suggestion from myself as President that he might well circulate it to all members of the Board of Governors, so that they can be ready for formal consideration of it at their meeting in Cleveland."

. . . There being no further business, the meeting adjourned at 3:50 p.m. . . .

Adjournment.

Attest: E. R. LOVELAND,
Secretary

THE STORY OF CLEVELAND

Site of the 33rd Annual Session of the American College of Physicians, April 21–25, 1952

ORIGINALLY a trading post at the mouth of the Cuyahoga River, Cleveland has developed as the industrial center of the historic "Western Reserve." This tract of land was part of the original Connecticut charter granted in 1662 by Charles II for the whole area between the forty-first and forty-second parallels westward to the Pacific Ocean. In 1786 Connecticut released to the United States title to all except one area which she reserved for herself and called the Connecticut Western Reserve.

FIG. 1. Cleveland Public Auditorium and the Mall. (Miller-Ertler Studios, Cleveland.)

Cleveland was developed as a planned real estate venture at the time of the great western trek into the Ohio country after the Revolution. The Public Square was laid out in 1796 by Moses Cleveland, Yale graduate and attorney. A group of hardy New England Yankees formed the Connecticut Land Company and raised a sum of $1,200,000. The names of this group have been handed down to succeeding generations whose descendants are still among the first families of Cleveland. Samuel Mather, Jr. was the direct forebear of the Samuel Mather who built the present $2,500,000 Western Reserve University Medical School.

Cleveland, the natural meeting place for iron ore, coal and limestone, grew rapidly. The Great Lakes iron ore deposits are the largest and richest in the world. Iron and steel have been Cleveland's leading industries since

1828 when the first smelter was established. Today a greater annual tonnage comes from the Great Lakes to Cleveland than that of Liverpool and more than all of the French ports combined.

Cleveland industry has become most diversified, having at present 3,163 industrial plants with an aggregate annual payroll in excess of $625,291,000 and products with an annual value of $3,180,000,000. Cleveland leads in the production of all manner of iron and steel products, hardware, paint, malleable castings, electrical machinery and lamps, sewing machines, tractors and auto parts, multigraphs, telescopes and ready-made clothing.

Education

Western Reserve University was established in 1826 at Hudson, twenty miles to the south; and in 1882 moved to Cleveland leaving the academy at Hudson. The University now has 11 colleges and 10,510 students including downtown Cleveland College. The Medical School is placed in the

Fig. 2. Severance Hall, the home of the Cleveland Orchestra.

center of a complete hospital group representing an investment of $13,000,000. The famous University Circle at East 107th Street and Euclid Avenue, 3½ miles east of the Public Square, includes in addition to the University, the Art Museum, Severance Hall, the Medical Library, and the Case Institute of Technology. In addition Cleveland has John Carroll University, Fenn College, 300 public and parochial schools and a group of special institutes for vocational training.

The Art Museum is an architectural gem in a colorful setting viewed from Euclid Avenue across the lagoon. The city's cultural maturity is attested further by the community interest in the drama. The Play House

at East 86th Street provides an outlet for local talent. The Cleveland Orchestra has done much to carry the story of Cleveland's educational and cultural progress to the rest of the world. Severance Hall at University Circle is the beautiful home of the Orchestra.

Unique among medical facilities in American cities is the Allen Memorial Medical Library Building at the corner of Adelbert Road and Euclid Avenue. This monumental structure was made possible by a gift from Mrs. Elizabeth Severance Prentiss in honor of one of the founders of the library, Dr. Dudley P. Allen, and is the official home of the practicing physicians of Cleveland. Besides the magnificent library, reading rooms and club rooms, the building houses the offices and headquarters of the Academy of Medicine (the county medical society) with auditorium facilities for groups of varying sizes. The Library, with 100,000 volumes, is one of the outstanding institutions of its kind in the country. The Academy of Medicine is a pioneer in the development of health education and community health planning in Cleveland. Its membership of nearly 2,400 carries on the work in scientific sections, in numerous committees, by appointees on various welfare boards throughout the city, and by the publication of a monthly bulletin which reaches interested individuals and groups in addition to the membership. The executive office, under the direction of a full-time executive secretary, correlates all activities, and in addition furnishes a twenty-four hour call and information service for the public and the patients of Academy members.

Hospitals

In Cuyahoga County there are 9,788 hospital beds exclusive of sanatoria. Greater Cleveland has a population of 905,636 giving an approximate ratio of hospital beds to population of 9 per 1,000. All cases of tuberculosis from Cleveland and Cuyahoga County are hospitalized by the Bureau of Tuberculosis of the Division of Health; they number at present 816 cases. Two hundred beds are maintained at the Contagious Division of City Hospital for quarantinable diseases.

Warrensville Farm for charitable and corrective purposes is a striking example of the spirit of Cleveland citizens. This great experiment, which has brought many students of social welfare to Cleveland, occupies 2,000 acres of high ground some seven miles from the city. Here tuberculous patients are cared for in the beautiful and well-equipped Sunny Acres Sanitarium; aged couples are enabled to spend their last years together in a cottage expressly for that purpose, and inmates of the House of Correction are taught useful occupations—in the shops in winter and in the farm fields in summer.

Likewise, Cleveland has pioneered in socio-economic measures in the medical field, especially in group hospitalization and a dispensary admissions plan widely adopted and copied in the United States. The Academy of Medicine is sincerely trying to develop sound measures to adjust the form

and cost of medical service to changing social needs. This policy from within the profession is regarded as the best prevention against meddlesome interference from without, especially by politically minded governmental agencies.

The University Hospitals of Cleveland is a non-profit corporation organized in 1925 which provides a consolidated management for four established hospitals—Lakeside Hospital, Maternity Hospital, Babies and Childrens Hospital, and Rainbow Hospital for Crippled and Convalescent Children. With the exception of Rainbow Hospital, the group is situated

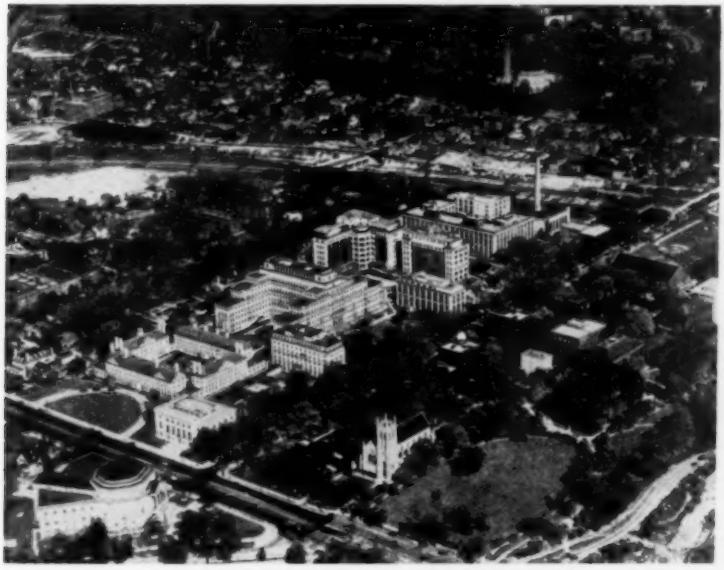


FIG. 3. The University Hospitals of Cleveland.

on the campus of Western Reserve University, with which the hospitals maintain a teaching affiliation. Here also are located the School of Medicine, the School of Dentistry and the Institute of Pathology where Dr. Harry Goldblatt did his work on hypertension and won the John Phillips prize of the College for 1938.

At Maternity Hospital, facilities are provided for the care of 75 private and 51 community service patients in the obstetrical division, and 34 patients on the gynecological service. Babies Dispensary and Hospital represent the pediatric department of the Medical School and have 75 beds. For the special benefits of its little patients, Rainbow Hospital, on Green Road, South Euclid, is built on the cottage, or one-floor plan. Convalescent care is given

to children crippled by infantile paralysis, bone tuberculosis, rheumatic heart disease and various nutritional deficiencies. Also, as early as 1929 Dr. Henry John established a camp for diabetic children, Camp Ho Mita Koda, the first fully organized camp of its kind in the world.

The City Hospital, 3395 Scranton Road, sixth largest general hospital in the United States, is a municipal institution owned and operated by the City of Cleveland. It was founded in 1837 and first occupied its Scranton Road site in 1855. The present hospital group, constructed largely since 1922, covers twenty-seven acres and includes sixteen buildings with facilities for the care of 1,036 patients. The General Building (722 beds) houses the

FIG. 4. Cleveland City Hospital.

medical and surgical services, pediatrics, obstetrics, electrocardiography, and x-ray. There are, in addition, separate buildings for Contagious Diseases (168 beds), Tuberculosis (351 beds), Psychopathic Diseases (307 beds), Pathology, and the Out-Patient Department.

City Hospital is affiliated with Western Reserve University and is a teaching unit of the Medical School. Since 1913 the University has assumed responsibility for the professional care of patients. Visiting staff members are nominated by the faculty of the School of Medicine. In this way it has been possible to assure patients scientific treatment and to carry on medical teaching undisturbed by the political contingencies of changing city administrations. The present professional staff comprises 175 attending physicians, 95 house physicians, and 500 nurses.

In addition to University and City Hospitals, medical students receive clinical instruction at Charity Hospital which was a pioneer institution dating

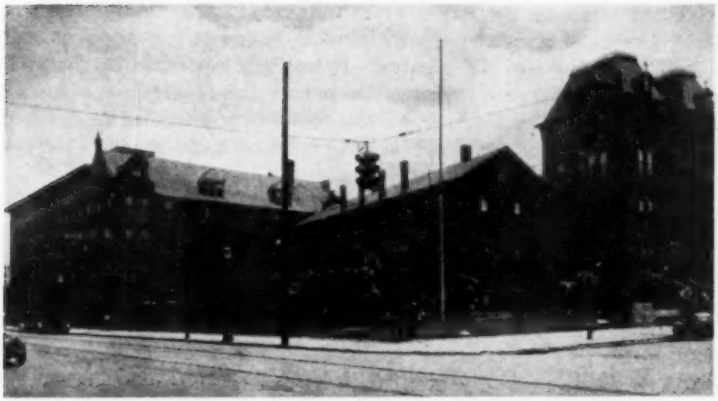


FIG. 5. Charity Hospital.

from the Civil War period and remains as the only downtown hospital in Cleveland. It has a capacity of 245 beds and is located on East 22nd Street four blocks south of Euclid Avenue. It has very important out-patient and emergency departments.

St. Luke's Hospital is a general hospital affiliated with the Methodist Episcopal Church and has a capacity of 467 beds to be expanded still further. It is beautifully located at the entrance to Shaker Heights, residential suburb of the City of Cleveland. The building was constructed in 1927 and occupies a spacious tract of sixteen and a half acres on Shaker Boulevard at

FIG. 6. St. Luke's Hospital.

East 115th Street on the Rapid Transit Railroad. The institution, representing a value of approximately $9,000,000, is one of the largest privately endowed institutions in the country. It was made possible by the gift of Mrs. Elizabeth Severance Prentiss as a memorial building in honor of Dr. Dudley P. Allen. The hospital provides complete professional service under the three main divisions of medicine, surgery and obstetrics, with a large and well developed department of pathology.

Mount Sinai Hospital, 1800 East 105th Street, is a non-sectarian hospital founded in 1916. The present capacity of the hospital is 388 beds and comprises complete facilities for general medical and surgical services and their sub-specialties. The hospital was enlarged in 1926 by the addition of

FIG. 7. Mt. Sinai Hospital.

a separate out-patient department building, a nurses' home, and laboratory for pathology. The professional staff comprises 214 attending physicians and 36 house physicians and 185 nurses. Served annually are 11,160 in-patients, 8,153 emergency patients, and 7,133 clinic patients. The hospital maintains a nurses' training school.

The Cleveland Clinic is located at Euclid Avenue and East 93rd Street. The Cleveland Clinic Foundation was organized by Dr. Frank E. Bunts, Dr. George Crile, Dr. William E. Lower and Dr. John Phillips, F.A.C.P., in February, 1921, under a charter from the State of Ohio. The Cleveland Clinic Building was opened on February 26, 1921. As the activities of the Clinic expanded and the interests of the Foundation broadened, other buildings were added, the Cleveland Clinic Hospital at present with 323 beds, the Power Plant and Laundry in 1926, the Research Building in 1928, the new Clinic Building in 1931. The buildings house Museums of Pathology, of

Intelligence, Power and Personality of Man and Animals, and of Comparative Anatomy and Physiology. There are 90 physicians on the staff and 120 fellows; nurses employed—150. The Cleveland Clinic represents an investment of $12,000,000.

St. Alexis Hospital is located in the steel mill district on the corner of Broadway and McBride Street. It is one of the city's older hospitals,

FIG. 8. Cleveland Clinic.

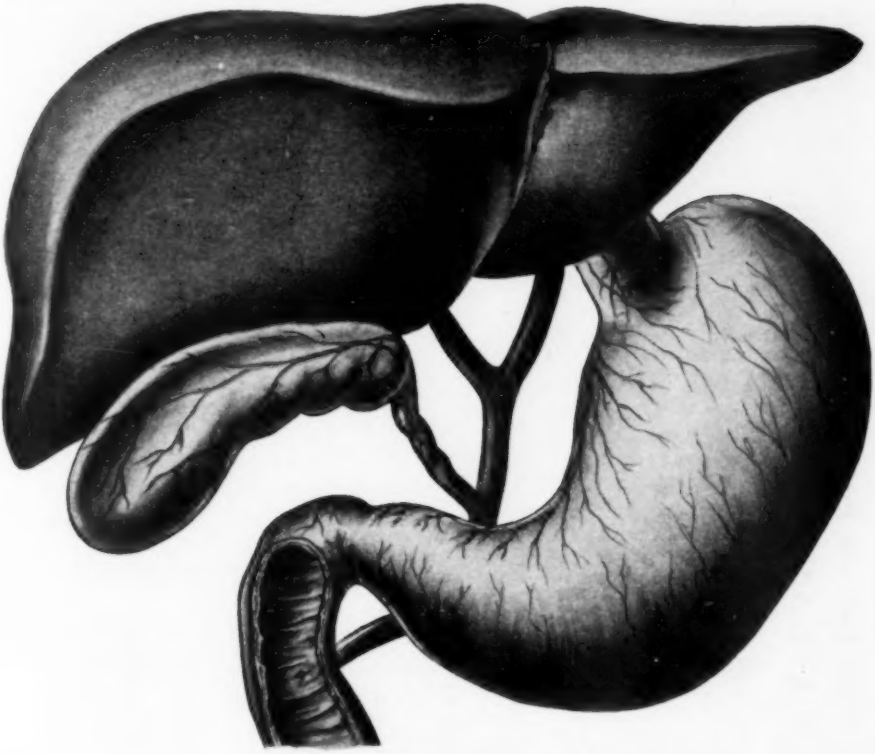
dating from 1884 and has a capacity of 234 beds. It renders invaluable service to the employees of the American Steel and Wire Company, the Republic, Ohio and other Steel Companies. All general hospital services are provided except obstetrics. The staff consists of 137 visitants and 13 interns and residents and 135 nurses.

The Cleveland Health Museum at 8811 Euclid Avenue, the first of its kind to be incorporated in the United States, has 521 physician members and a suitable building.

The Convention Hall

The General Sessions of the College of Physicians will be held in the Public Auditorium (figure 1). This is one of the first structures of its kind, built at a cost of $15,000,000. Its range of service is practically unlimited. Sixteen events can be held simultaneously and without interference. The Main Auditorium seats 12,500 persons and can be readily adapted for the sessions of a huge convention. The beautiful Music Hall seats 3,000 and is well adapted to the needs of the College. The Ball Room and Little Theatre have seating capacities of 1,500 and 700 respectively; and ten other halls range in seating capacity from 90 to 500. A common stage makes it possible for the Main Auditorium and the Music Hall to seat 16,000 persons for a single event. The building is of fireproof construction and designed in Italian Renaissance architecture. The color and the diffused lighting in the main auditorium lend a warmth and softness unusual in buildings of such immense proportions. The Auditorium's acoustics have been declared perfect. The $100,000 pipe organ is one of the finest in America. Among other features of the building are spacious lobbies and corridors, wide ramps and stairways, committee rooms, lockers, telephone booths, women's and men's retiring rooms, emergency hospital, checkroom and telegraph stations. The Hall is ideally located in the heart of the downtown district within easy walking distance of all principal hotels and shops.

Cleveland is expecting a record attendance at the 1952 Annual Session of the American College of Physicians. The Western Reserve University Medical School, the hospitals and the Officers of the College, are planning a program that will be in keeping with a record attendance and with the traditions of Cleveland medicine.



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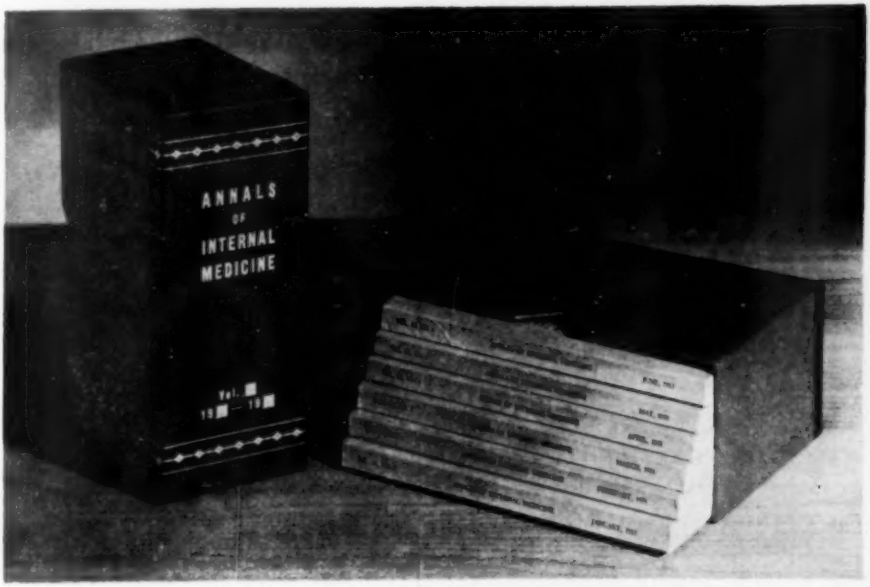

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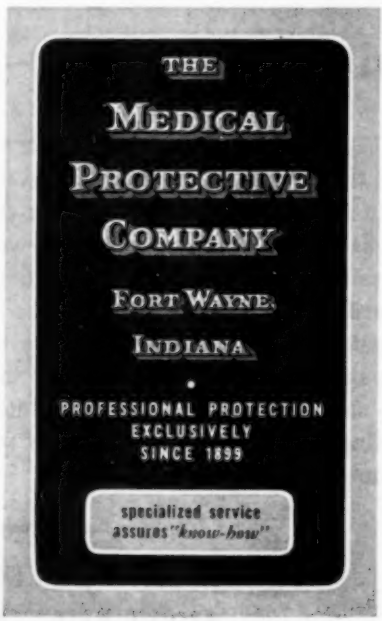

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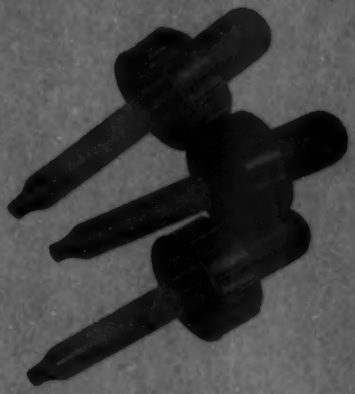

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